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Bioorganic & Medicinal Chemistry
Bioorganic & Medicinal Chemistry 15 (2007) 3548–3564

Synthesis and SAR studies of a novel class of $S1P_1$ receptor antagonists

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Received 27 September 2006; revised 22 February 2007; accepted 23 February 2007
Available online 3 March 2007

Abstract—A series of Sodium 4-[(4-butoxyphenyl)thio]-2′-substituted-1,1′-biphenyl-3- sulfonates were identified as functional sphingosine-1-phosphate (S1P) antagonists with selectivity for the $S1P_1$ receptor subtype starting from chemical lead **2**, which was found while screening our in-house compound library. We performed chemical modifications on each regional structure of compound **2**, for example, on the three ring compartments, the benzyl substituents, and the long alkyl chain part. The introduction of a biphenyl skeletal structure and the installation of a hydroxyl group onto the terminal carbon in the side-chain region resulted in the potent derivative **35c**, which showed >500-fold more potent $S1P_1$ inhibitory activity than lead compound **2**. We report herein the synthesis and structure–activity relationships of structurally novel $S1P_1$ receptor antagonists.

1. Introduction

Sphingosine-1-phosphate (S1P) receptors were identified as a family of G-protein coupled receptors and were subdivided into five subtypes ($S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$, $S1P_5$), which are coupled differentially via G_i, G_q, $G_{12/13}$, and Rho to multiple effector systems whose signaling pathways are linked to transcription factor activation, cytoskeletal proteins, adhesion molecule expression, and caspase activities.[1] Through these signaling pathways, S1P receptors can affect diverse biological responses, including mitogenesis, differentiation, migration, and apoptosis, and thus are supposed to be involved in a variety of pathological conditions such as angiogenesis, inflammation, and cardiovascular diseases.[2] Among the widespread investigations to seek seeds for various therapeutic agents targeting S1P receptors,[3] $S1P_1$ receptor antagonists[4] are expected to be effective therapeutic agents for the cardiovascular disease and angiogenesis caused by mitogenic cell growth.[5]

Herein, we report on the synthesis of a novel class of S1P receptor antagonists, particularly $S1P_1$ antagonists, and their structure–activity relationships.

Our discovery process for a subtype-selective $S1P_1$ receptor antagonist started with the screening of our in-house compound library. Sodium 2-(4-ethoxyphenoxy)-5-(3-octadecyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl) benzenesulfonate (**2**) was found as the new chemical lead during the screening. Chemical lead **2** possesses three ring compartments (defined as the A, B, and C rings, as shown in Fig. 1), a long saturated alkyl chain region, and a sulfonic acid group on the B ring part as representative structural features. Its lipid-like structure, featuring both a long alkyl chain part and a negative ionizable sulfonic acid group, recalls a structural resemblance to sphingosine-1-phosphate (S1P) **1**. Compound **2** showed moderate human $S1P_1$ antagonistic activity ($IC_{50} = 17.0\ \mu M$) in cAMP assays in human $S1P_1$ receptors stably expressed in Chinese hamster ovary (CHO) cell membranes. Our initial effort was

Keywords: Sphingosine-1-phosphate; S1P receptor; Antagonist; Structure–activity relationships.
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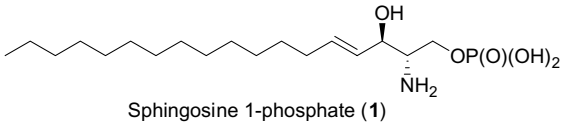
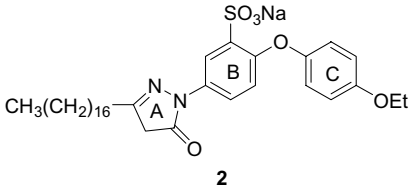
doi:10.1016/j.bmc.2007.02.048



Sphingosine 1-phosphate (**1**)



2

Figure 1. Structures of sphingosine-1-phosphate and chemical lead 2.

directed at improving the $S1P_1$ antagonist activity along with defining the key structural elements required for this activity.

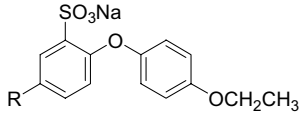
2. Chemistry

The test compounds listed in Tables 1–4 were synthesized as outlined in Schemes 1–4.

The synthesis of **11a**, **12a**, **13a**, and **14a**–**c** is described in Scheme 1. To begin, sulfonic acid **3** was treated with ethoxyphenol in the presence of LiOH in DMSO to afford biphenyl ether **4a**–**c**. The nitro group of **4a**–**c** was reduced to an amino group by using Pd on carbon as a catalyst in MeOH under a hydrogen atmosphere. The obtained amine **5a**–**c** was treated with $NaNO_2$ and aqueous HBF_4 in EtOH, which afforded diazo species **6a**–**c**, and successive treatments of various aryl boric acids and a catalytic amount of $Pd(OAc)_2$ each gave the aldehydes **7a**, **8a**, **9a**, and **10a**–**c**. The creation of a side-chain moiety via a 1,2-addition reaction with 1-dodec-1-yn-1-yllithium proceeded smoothly to afford secondary alcohols, which were purified by silica gel column chromatography to give **11a**, **12a**, **13a**, and **14a**–**c**.

To investigate the SAR of the 4-ethoxyphenoxy moiety of compound **14a**, we turned our attention to the preparation of thiophenylether derivatives. The synthetic route of compounds **20a**–**f** is shown in Scheme 2. Phenyl

Table 1. $S1P_1$ antagonistic activities of A ring and alkyl chain variations **11a**–**14a**



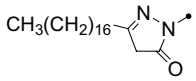
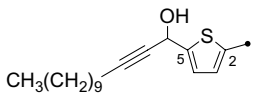
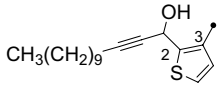
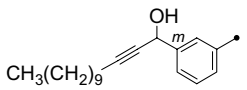
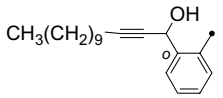
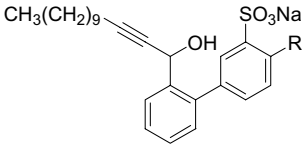
Compound	R	IC_{50} (μM)
2		17.0
11a		5.5
12a		1.3
13a		4.6
14a		0.40

Table 2. $S1P_1$ antagonistic activities of the variation of the C ring part



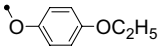
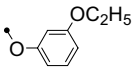
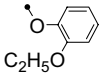
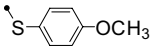
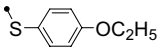
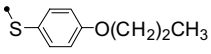
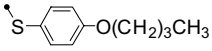
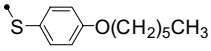
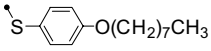
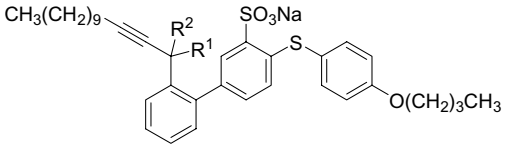
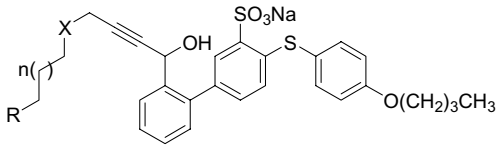
Compound	R	IC_{50} (μM)
14a		0.40
14b		>17.0
14c		8.9
20a		0.70
20b		0.40
20c		0.19
20d		0.19
20e		0.52
20f		>2.4

Table 3. $S1P_1$ antagonistic activities of the variation in the substituent on the benzyl position



Compound	R^1	R^2	IC_{50} (μM)
20d	H	OH	0.19
25a	H	NH_2	0.37
25b	H	H	>8.1
25c	CH_3	OH	1.0

Table 4. $S1P_1$ antagonistic activities of side-chain variations



Compound	X	*n*	R	IC_{50} (μM)
20d	CH_2	6	CH_3	0.19
34	CH_2	6	OH	0.080
35a	O	1	OH	>20
35b	O	3	OH	0.34
35c	O	5	OH	0.031
35d	O	7	OH	0.098
35e	O	9	OH	0.13

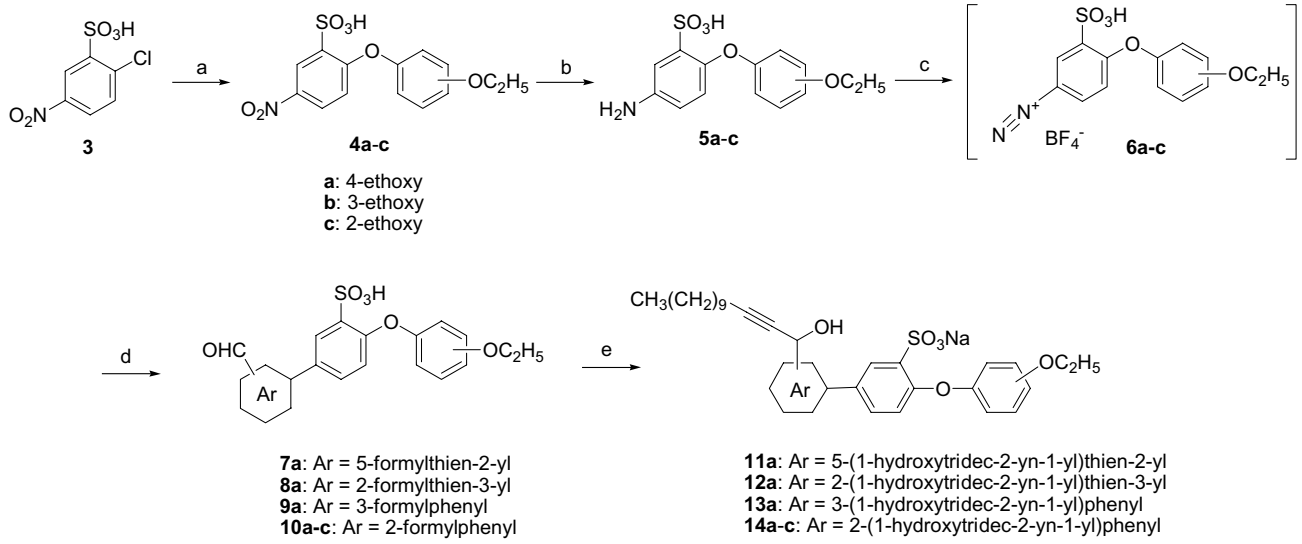
2,5-dibromobenzene sulfonate **15** was the starting material[6] and was treated with 4-hydroxythiophenol in the presence of triethylamine in DMF to afford thioether **16**, whose phenolic hydroxyl group was alkylated by treatment with alkylhalide and DBU in DMF to provide **17a**–**f**. A Suzuki coupling reaction of bromide **17a**–**f** with 2-formylbenzeneboric acid proceeded smoothly in the presence of a catalytic amount of $Pd(PPh_3)_4$ and aqueous K_2CO_3 in DME to give the key intermediate aldehyde **18a**–**f**. The 1,2-addition reaction of **18a**–**f** with 1-dodec-1-yn-1-yllithium afforded propargyl alcohol **19a**–**f** smoothly, and saponification with aqueous NaOH in dioxane afforded the corresponding sodium salt of sulfonic acid **20**. The variations in each structural region could be synthesized using key reactive intermediates such as compounds **18** and **19**.

The variation on the benzyl position of the A ring moiety could be synthesized in the manner shown in Scheme 3. The secondary hydroxyl group of **19d** was esterified by treatment with Ac_2O and Et_3N in CH_2Cl_2 to afford acetate **21**. The acetoxy group of **21** could be converted alternatively to a hydrogen or phenylcarbamate group by treatment with a combination of trifluoroacetic acid and triethylsilane, or $BF_3{\cdot}OEt_2$ and phenylcarbamate in CH_2Cl_2, respectively. On the other hand, compound **19d** was oxidized with Dess–Martin periodinane in CH_2Cl_2 to give ketone **23**, which was treated with methyl magnesium bromide in THF to afford tertiary alcohol **24**. The obtained phenyl sulfonates **22a**,**b** and **24** were saponified with aqueous NaOH in dioxane to afford the corresponding sodium salt of sulfonic acid **25a**–**c**.

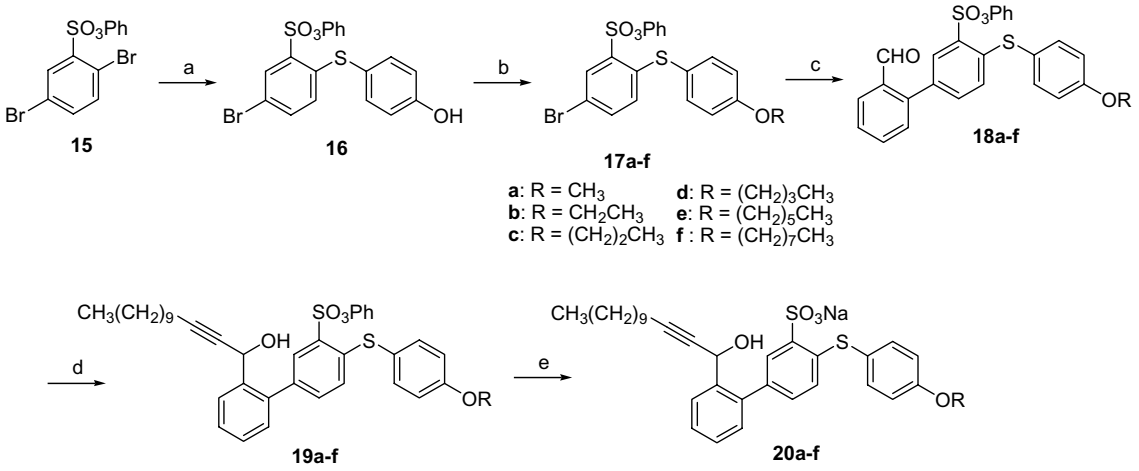
The synthetic route of the variations of the side-chain moiety is shown in Scheme 4. The alkyne **26** was treated with 3,4-dihydro-2*H*-pyran in CH_2Cl_2 in the presence of *p*-TsOH to give **27**. The propargyl ethers **29a**–**e** were also easily synthesized by alkylation of the hydroxy group of propargylalcohol **28** with various alkyl bromides.[7] Each prepared alkyne part was treated with *n*-BuLi in THF, and the resulting alkynyl lithium solution was treated with aldehyde **18d** to obtain the secondary alcohols **30** and **31a**–**e**. The tetrahydropyranyl group on the terminal hydroxyl group was deprotected by treatment with PPTS in MeOH to afford diols **32** and **33a**–**e**, whose phenyl sulfonate groups were hydrolyzed by treatment with aqueous NaOH in dioxane to afford the corresponding sodium salt of sulfonic acid **34** and **35a**–**e**.

3. Results and discussion

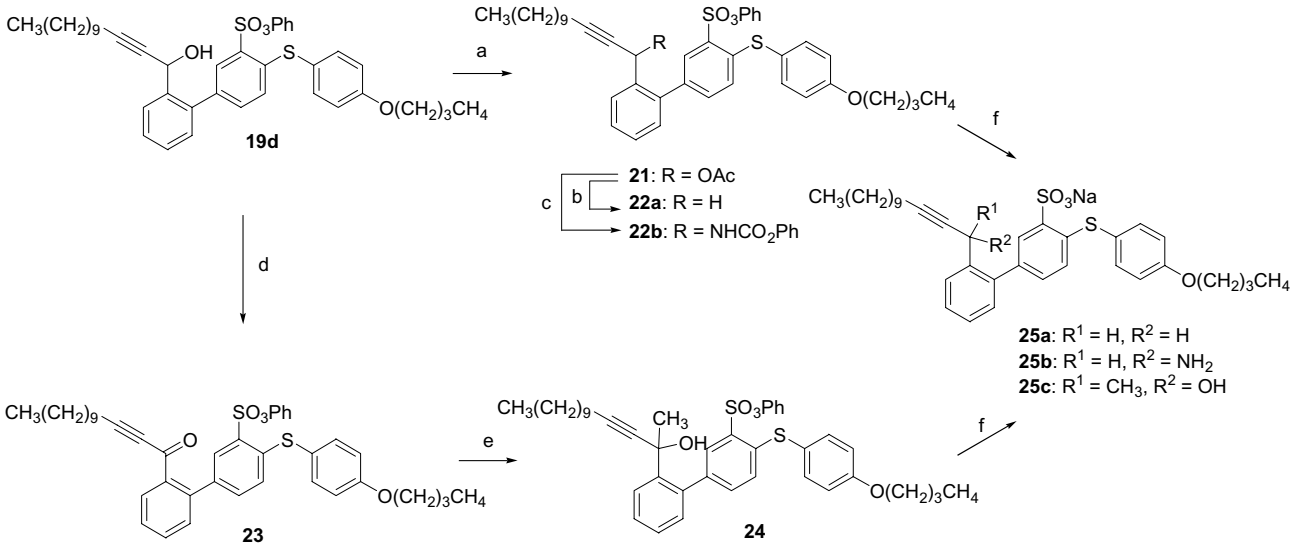
The compounds listed in Tables 1–4 were biologically evaluated for their antagonistic activities in cAMP assays[8] in human $S1P_1$ receptors stably expressed in Chinese hamster ovary (CHO) cell membranes. During the course of our in-house compound library screening, compound **2** was found to show moderate activity. Replacement of the long alkyl chain substituted pyrazolone ring of **2** with thiophene and a benzene ring afforded **11**–**14a**, which showed more potent inhibitory activities, as shown



Scheme 1. Reagents: (a) ethoxyphenol, LiOH, DMSO; (b) H_2, Pd–C, MeOH; (c) $NaNO_2$, 48% aq HBF_4, EtOH; (d) arylboric acid, $Pd(OAc)_2$, MeOH; (e) 1-dodecyne, *n*-BuLi, THF.



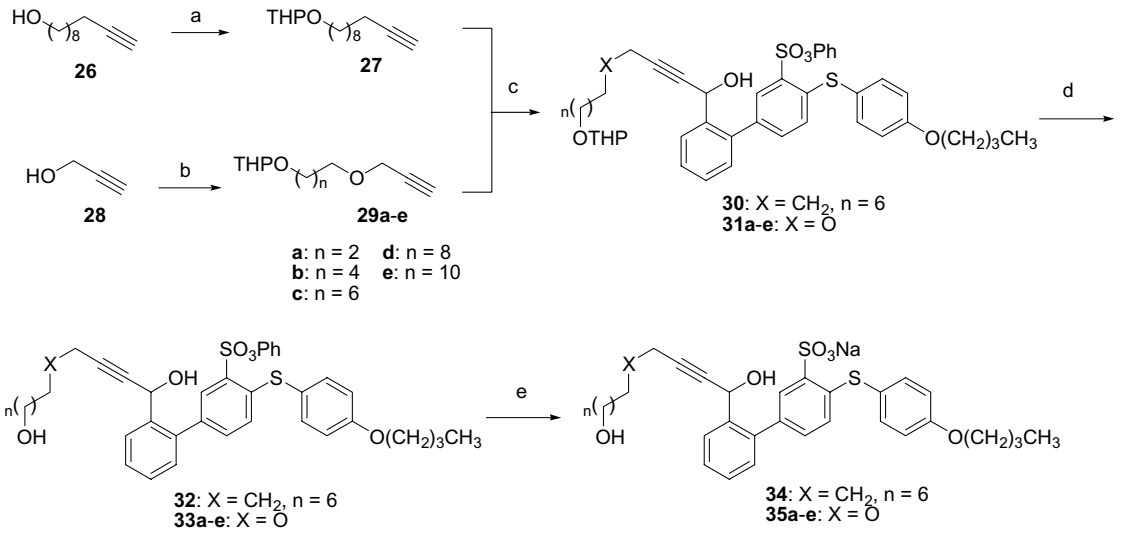
Scheme 2. Reagents: (a) 4-hydroxythiophenol, Et_3N, DMF; (b) alkylhalide, DBU, DMF; (c) 2-formylbenzeneboric acid, $Pd(PPh_3)_4$, aq K_2CO_3, DME; (d) 1-dodecyne, *n*-BuLi, THF; (e) aq NaOH, dioxane.



Scheme 3. Reagents: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (b) triethylsilane, CF_3CO_2H, CH_2Cl_2; (c) H_2NCO_2Ph, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (d) Dess–Martin periodinane, CH_2Cl_2; (e) MeMgBr, THF; (f) aq NaOH, dioxane.

in Table 1. Due not only to the enhanced effect of $S1P_1$ affinity, but also to the synthetical advantage of alkynyl side-chain derivatives, we shifted focus to propargyl alcohol analogs. Thiophene analogs **11a** and **12a** and benzene analogs **13a** and **14a** showed the same tendency to display structure–activity relationships in the A ring. Namely, thiophene analog **12a**, whose thiophene ring bridges between the B ring part and side-chain part at the 1- and 2-positions, showed 4-fold higher affinity than the 2- and 5-position bridging thiophene analog **11a**. Furthermore, the *ortho* bridging benzene analog **14a** also showed 11-fold more potent IC_{50} values than the *meta* conjoining benzene derivative **13a**. These observations suggested that the conjoining position of the side-chain region on the A ring strongly affected the $S1P_1$ affinity, and it was then maximized with the *ortho*-substituted benzene derivative **14a**, which exhibited 40-fold more potent $S1P_1$ antagonist activity than lead compound **2**.

Next, investigations around the SAR of the 4-ethoxyphenoxy moiety of compound **14a** were performed and are summarized in Table 2. The transposition of the ethoxy group onto the *meta*- or *ortho*-position decreased the affinity to the $S1P_1$ receptor (compound **14a** vs **14b** and **14c**). Oxo-ether **14a** and thio-ether **20b** showed almost equal IC_{50} values, suggesting that the tethering atom between the B and C ring parts did not affect $S1P_1$ affinity. In the variation of the alkoxy group on *para*-position **20a–f**, the $S1P_1$ receptor affinity was moderately affected by the alkyl chain length of the alkoxy group, and was maximized at a chain length of 3–4 carbon atoms (compounds **20c** and **20d**). The synthetic advantage of the thio-ether analog prompted us to fix the C ring moiety as a *p*-butoxy phenylthio group. We



Scheme 4. Reagents: (a) 3,4-dihydro-2*H*-pyran, *p*-TsOH, CH_2Cl_2; (b) bromide, NaH, DMF; (c) *n*-BuLi, THF then aldehyde **18d**; (d) PPTS, MeOH; (e) aq NaOH, dioxane.

then turned our attention to defining the effect of the key polar functional groups in the structure of compound **20d**.

In the scaffold of compound **20d**, the effects of the substituents on the benzyl position are summarized in Table 3. The amino derivative **25a** was found to retain its $S1P_1$ inhibitory activity, although it did not improve the activity compared to the hydroxy analog **20d**. The $S1P_1$ antagonistic activity of compound **25b**, which possesses a hydrogenated structure on the benzyl position, decreased drastically. The tertiary alcohol **25c** also showed moderately weaker activity than **20d**, confirming that the secondary hydroxy group on the benzyl position of the A ring part of **20d** was the accommodating structure.

The results of the derivatization on the side-chain region are summarized in Table 4.

Surprisingly, introducing a hydroxy group onto the terminal carbon in the side-chain region clearly enhanced $S1P_1$ antagonistic activity. Diol derivative **34** showed 2-fold more potent $S1P_1$ antagonistic activity than basic compound **20d**. In the derivatives of propargyl ether **35a**–**e**, the alkyl chain length significantly affected their activities, which were maximized at $n = 5$ (compound **35c**).

Both compound **20d** and hydroxylated analog **35c** were further profiled for selectivity among S1P receptors. The antagonistic activities of these two compounds for $S1P_1$, $S1P_2$, $S1P_3$, and $S1P_4$ in FLIPR assays[9] in S1P receptors stably expressed in Chinese hamster ovary (CHO) cell membranes are summarized in Table 5.

Both compounds **20d** and **35c** possess slightly $S1P_1$ selective inhibitory profiles. Comparisons with compound **35c** clearly showed that the terminal hydroxy group on the side-chain part evenly enhanced the inhibitory activity for each receptor.

Table 5. Antagonistic activities of compounds **20d** and **35c** for $S1P_1$, $S1P_2$, $S1P_3$, and $S1P_4$

Compound	IC_{50} (μM)			
	$S1P_1$	$S1P_2$	$S1P_3$	$S1P_4$
20d	1.0	24	13	40
35c	0.5	11	5	6

4. Conclusions

Starting from the novel sulfonic acid derivative **2**, identified via high-throughput screening, a SAR was established and the key structural requirements for activity were determined. Exploratory derivatization, focusing on each regional structure of compound **2**, revealed that the conjunction pattern between the long alkyl chain and the A ring part directly affected the antagonistic activity for $S1P_1$ receptor. We could then obtain the biphenyl analog **20d**, which exhibited 80-fold more potent $S1P_1$ antagonistic activity than compound **2**. Further SAR studies on the scaffold of compound **20d** clarified that the hydroxyl group on the terminal position of the long alkyl chain evenly enhanced the affinity for each of the S1P receptors, and its activity was slightly $S1P_1$ selective. The most potent $S1P_1$ antagonist in this article, **35c**, showed sub-micro order $S1P_1$ antagonistic activity. Further derivatization based on the structure of the compounds described in this article is in progress in order to improve their pharmacokinetic profiles and enhance their $S1P_1$ antagonistic activities.

5. Experimental

All melting points were measured with a Yanaco MP-500D micro melting point apparatus and are uncorrected. The IR spectra were measured with a JASCO FT/IR 8900 spectrophotometer, and the peaks were recorded in cm^{-1}. ^1H NMR spectra were recorded on a Varian Mercury 400 or 500 spectrometer, with tetra-

methylsilane as an internal reference. The mass spectra were recorded using a JEOL JMS-BU 20 or JMS-700 spectrometer. High-resolution mass (HRMS) spectroscopy was carried out with a JEOL JMS-700V mass spectrometer. Thin-layer chromatography (TLC) was used routinely to monitor the progress and the purity of the compounds and was performed on Merck Kieselgel 60 F_{254} plates. For the flash column chromatography, silica gel (Kieselgel 60, 230–400 mesh) was employed.

5.1. 2-(4-Ethoxyphenoxy)-5-nitrobenzenesulfonic acid (4a)

$LiOH{\cdot}H_2O$ (17.2 g, 712 mmol) was added to a solution of 2-chloro-5-nitrobenzenesulfonic acid **3** (57.0 g, 240 mmol) and 4-ethoxyphenol (49.7 g, 360 mmol) in DMSO (215 ml) at room temperature. After stirring for 0.5 h at 110 °C, the reaction mixture was evaporated in vacuo. Concd HCl (30 ml) and water (430 ml) were added to the obtained residue, and the resulting mixture was purified by ODS (Cosmosil $75C_{18}$-PREP) column chromatography (eluent, H_2O/MeOH = 9:1–65:35) to afford the title compound (60.6 g, 75%) as a white crystalline solid. Mp 338–350 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (t, 3H, J = 7.0 Hz), 4.04 (q, 2H, J = 7.0 Hz), 6.78 (d, 1H, J = 6.8 Hz), 6.99–7.06 (m, 4H), 8.13 (dd, 1H, J = 6.8 Hz, 2.9 Hz), 8.58 (d, 1H, J = 2.9 Hz).

5.2. 2-(3-Ethoxyphenoxy)-5-nitrobenzenesulfonic acid (4b)

The title compound was synthesized in the same manner as the general procedure for compound **4a**. ^{1}H NMR (400 MHz, CD_3OD) δ 1.43 (t, 3H, J = 7.0 Hz), 4.04 (q, 2H, J = 7.0 Hz), 6.69 (t, 1H, J = 2.3 Hz), 6.72 (dd, 1H, J = 8.1 Hz, 2.3 Hz), 6.87 (dd, 1H, J = 8.4 Hz, 2.3 Hz), 7.04 (d, 1H, J = 9.2 Hz), 7.20–7.24 (m, 2H), 7.27–7.32 (m, 1H), 7.33–7.40 (m, 3H), 8.36 (dd, 1H, J = 9.2 Hz, 2.8 Hz), 8.81 (d, 1H, J = 2.8 Hz); IR (thin film) 1607, 1579, 1528, 1488, 1470 cm^{-1}.

5.3. 2-(2-Ethoxyphenoxy)-5-nitrobenzenesulfonic acid (4c)

The title compound was synthesized in the same manner as the general procedure for compound **4a**. ^{1}H NMR (400 MHz, CD_3OD) δ 1.25 (t, 3H, J = 7.0 Hz), 4.08 (q, 2H, J = 7.0 Hz), 6.85 (d, 1H, J = 9.2 Hz), 7.06 (td, 1H, J = 7.8 Hz, 1.4 Hz), 7.09 (dd, 1H, J = 7.8 Hz, 1.4 Hz), 7.23 (dd, 1H, J = 1.7 Hz, 7.8 Hz), 7.26–7.36 (m, 6H), 8.31 (dd, 1H, J = 9.2 Hz, 2.8 Hz), 8.72 (d, 1H, J = 2.8 Hz); IR (thin film) 1605, 1526, 1498, 1471, 1380 cm^{-1}.

5.4. 5-Amino-2-(4-ethoxyphenoxy) benzenesulfonic acid (5a)

7.5% Pd–C (8.7 g) was added to a solution of 2-(4-ethoxyphenoxy)-5-nitrobenzenesulfonic acid **4a** (60.6 g, 196 mmol) in H_2O (350 ml) and MeOH (350 ml), and the air was replaced with hydrogen. After stirring for 2.5 h at room temperature, the reaction mixture was filtered through Celite, and the filtrate was evaporated in vacuo. The obtained residue was recrystallized from MeOH (90 ml) and acetonitrile (1000 ml) to afford the title compound (52.4 g, 95%) as a white crystalline solid. Mp 285–300 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (t, 3H, J = 7.0 Hz), 3.95 (q, 2H, J = 7.0 Hz), 6.46–6.49 (m, 2H), 6.78–6.84 (m, 4H), 7.11 (d, 1H, J = 2.9 Hz); IR (KBr) 3453, 2980, 2930, 2623, 1616, 1567, 1478 cm^{-1}; MS (FAB) m/z: 308 $(M-H)^-$.

5.5. 5-Amino-2-(3-ethoxyphenoxy) benzenesulfonic acid (5b)

The title compound was synthesized in the same manner as the general procedure for compound **5a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, 3H, J = 7.0 Hz), 3.73 (br s, 2H), 3.98 (q, 2H, J = 7.0 Hz), 6.55–6.60 (m, 2H), 6.62–6.67 (m, 1H), 6.85 (dd, 1H, J = 8.8 Hz, 2.8 Hz), 6.92 (d, 1H, J = 8.8 Hz), 7.15–7.26 (m, 5H), 7.27–7.34 (m, 2H); IR (thin film) 3475, 3385, 1627, 1588, 1487, 1368 cm^{-1}.

5.6. 5-Amino-2-(2-ethoxyphenoxy) benzenesulfonic acid (5c)

The title compound was synthesized in the same manner as the general procedure for compound **5a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.0 Hz), 3.59 (br s, 2H), 4.08 (q, 2H, J = 7.0 Hz), 6.64 (d, 1H, J = 8.8 Hz), 6.77 (dd, 1H, J = 8.8 Hz, 2.9 Hz), 6.94 (td, 1H, J = 7.9 Hz, 1.5 Hz), 7.01 (dd, 1H, J = 7.9 Hz, 1.5 Hz), 7.08 (dd, 1H, J = 7.9 Hz, 1.7 Hz), 7.12 (d, 1H, J = 2.9 Hz), 7.15 (td, 1H, J = 7.9 Hz, 1.7 Hz), 7.20–7.26 (m, 1H), 7.28–7.35 (m, 4H); IR (KBr) 3386, 1625, 1490, 1371 cm^{-1}.

5.7. Sodium 4-(4-ethoxyphenoxy)-2′-(1-hydroxytridec-2-yn-1-yl)biphenyl-3-sulfonate (14a)

48% aqueous HBF_4 solution (5 ml) was added to the solution of 5-amino-2-(4-ethoxyphenoxy) benzenesulfonic acid **5a** (1.0 g, 3.2 mmol) in EtOH (5 ml), and $NaNO_2$ (0.89 g, 13.0 mmol) was added to the resulting solution at 0 °C. After stirring for 0.5 h, the precipitate was filtered off to afford the crude compound **6a**, which was dissolved in MeOH (3.5 ml). 2-Formylphenylboronic acid (0.63 g, 4.2 mmol) and $Pd(OAc)_2$ (94 mg, 0.42 mmol) were added to the reaction mixture at room temperature. After stirring for 2 h, the reaction mixture was filtered through Celite and the filtrate was evaporated in vacuo. The residue obtained was purified by short column chromatography on silica gel (eluent, MeOH/CH_2Cl_2 = 1:5) to afford the crude compound **10a** (0.18 g). A solution of crude compound **10a** in THF (1.0 ml) was added to a mixture of 1-dodecyne (0.20 ml, 1.2 mmol) and 1.6 M solution of n-BuLi in hexane (0.85 ml, 1.4 mmol) in THF (5 ml) at 0 °C. After stirring for 0.5 h at room temperature, 1 M aqueous NaOH (2.0 ml) was added to the reaction mixture and evaporated in vacuo. The obtained residue was purified by thin layer chromatography on silica gel (MeOH/CH_2Cl_2 = 1:5) to afford the title compound (77 mg, 30%) as an amorphous solid. ^{1}H NMR (400 MHz, CD_3OD) δ 0.89 (t, 9H, J = 6.6 Hz), 1.26–1.35 (brs, 14H), 1.40 (t, 3H, J = 7.3 Hz), 1.43–1.49 (m, 2H), 2.20 (dt, 2H, J = 2.2 Hz, 7.3 Hz), 4.03 (q, 2H, J = 6.6 Hz),

5.33 (d, 1H, J = 2.2 Hz), 6.93 (d, 2H, J = 9.5 Hz), 7.13 (d, 2H, J = 9.5 Hz), 7.21 (dd, 1H, J = 1.5 Hz, 8.8 Hz), 7.33–7.39 (m, 3H), 7.79 (dd, 1H, J = 1.5 Hz, 8.8 Hz), 7.97 (d, 1H, J = 2.2 Hz); IR (KBr) 3392, 2925, 1473, 1232 cm^{-1}; HRMS (ESI, negative) calcd for $C_{33}H_{39}O_6S$ $(M-H)^-$ 563.2467; obsd 563.2465.

5.8. Sodium 2-(4-ethoxyphenoxy)-5-[5-(1-hydroxytridec-2-yn-1-yl)-2-thienyl]benzenesulfonate (11a)

The title compound (76 mg, 45% from **5a**) was synthesized in the same manner as the general procedure for compound **14a**. ^1H NMR (400 MHz, CD_3OD) δ 0.88 (t, 3H, J = 6.8 Hz), 1.20–1.35 (m, 15H), 1.38 (t, 3H, J = 6.8 Hz), 1.40–1.60 (m, 4H), 2.29 (dt, 2H, J = 6.8 Hz, 2.0 Hz), 4.03 (q, 2H, J = 6.8 Hz), 5.56 (br, 1H), 6.76 (d, 1H, J = 8.8 Hz), 6.92 (d, 2H, J = 8.8 Hz), 7.06 (d, 1H, J = 3.7 Hz), 7.09 (d, 2H, J = 8.8 Hz), 7.17 (d, 1H, J = 3.7 Hz), 7.55 (dd, 1H, J = 8.8 Hz, 2.0 Hz), 8.19 (d, 1H, J = 2.0 Hz).

5.9. Sodium 2-(4-ethoxyphenoxy)-5-[3-(1-hydroxytridec-2-yn-1-yl)-2-thienyl]benzenesulfonate (12a)

The title compound (59 mg, 35% from **5a**) was synthesized in the same manner as the general procedure for compound **14a**. ^1H NMR (400 MHz, CD_3OD) δ 0.90 (t, 3H, J = 6.8 Hz), 1.24–1.35 (m, 15H), 1.40 (t, 3H, J = 6.8 Hz), 1.50 (m, 2H), 2.16 (s, 1H), 2.23 (t, 2H, J = 6.8 Hz), 4.04 (q, 2H, J = 6.8 Hz), 5.57 (s, 1H), 6.80 (d, 1H, J = 8.8 Hz), 6.94 (d, 2H, J = 8.8 Hz), 7.05 (d, 1H, J = 4.9 Hz), 7.11 (d, 2H, J = 8.8 Hz), 7.38 (d, 1H, J = 4.9 Hz), 7.48 (dd, 1H, J = 8.8 Hz, 2.0 Hz), 8.07 (d, 1H, J = 2.0 Hz).

5.10. Sodium 4-(4-ethoxyphenoxy)-3′-(1-hydroxytridec-2-yn-1-yl)biphenyl-3-sulfonate (13a)

The title compound (172 mg, 53% from **5a**) was synthesized in the same manner as the general procedure for compound **14a**. ^1H NMR (400 MHz, CD_3OD) δ 0.88 (t, 3H, J = 6.8 Hz), 1.16–1.33 (m, 15H), 1.39 (t, 3H, J = 7.8 Hz), 1.53 (quintet, 2H, J = 6.8 Hz), 2.27 (t, 2H, J = 5.9 Hz), 4.03 (q, 2H, J = 7.3 Hz), 4.58 (brs, 1H), 5.43 (brs, 1H), 6.83 (d, 2H, J = 8.8 Hz), 6.93 (d, 2H, J = 8.8 Hz), 7.11 (d, 2H, J = 8.8 Hz), 7.40 (d, 2H, J = 8.1 Hz), 7.48 (d, 1H, J = 7.3 Hz), 7.54 (d, 1H, J = 7.3 Hz), 7.59 (d, 1H, J = 7.3 Hz), 7.60 (d, 1H, J = 8.1 Hz), 7.75 (s, 1H).

5.11. Sodium 4-(3-ethoxyphenoxy)-2′-(1-hydroxytridec-2-yn-1-yl)biphenyl-3-sulfonate (14b)

The title compound (19 mg, 41% from **5b**) was synthesized in the same manner as the general procedure for compound **14a**. ^1H NMR (400 MHz, CD_3OD) δ 0.88 (t, 3H, J = 6.9 Hz), 1.26 (brs, 12H), 1.37 (t, 3H, J = 7.0 Hz), 1.38–1.46 (m, 2H), 1.48–1.57 (m, 2H), 2.28 (dt, 2H, J = 6.9 Hz, 2.0 Hz), 4.01 (q, 2H, J = 7.0 Hz), 4.56 (brs, 1H), 5.44 (s, 1H), 6.67–6.74 (m, 2H), 6.75 (t, 1H, J = 2.3 Hz), 6.93 (d, 1H, J = 8.5 Hz), 7.24 (t, 1H, J = 8.2 Hz), 7.42 (t, 1H, J = 7.7 Hz), 7.49 (t, 1H, J = 7.7 Hz), 7.56 (1H, J = 7.7 Hz), 7.62 (dd, 1H, J = 8.5 Hz, 2.4 Hz), 7.77 (s, 1H), 8.25 (d, 1H, J = 2.4 Hz); IR (KBr) 1587, 1606, 2854, 2926, 3409 cm^{-1}; HRMS (ESI, positive) calcd for $C_{33}H_{39}Na_2O_6S$ $(M+Na)^+$ 609.2263; obsd 609.2260.

5.12. Sodium 4-(2-ethoxyphenoxy)-2′-(1-hydroxytridec-2-yn-1-yl)biphenyl-3-sulfonate (14c)

The title compound (15 mg, 26% from **5c**) was synthesized in the same manner as the general procedure for compound **14a**. ^1H NMR (400 MHz, CD_3OD) δ 0.88 (t, 3H, J = 6.9 Hz), 1.25 (t, 3H, J = 7.0 Hz), 1.26 (brs, 12H), 1.37–1.46 (m, 2H), 1.48–1.57 (m, 2H), 2.27 (dt, 2H, J = 6.9 Hz, 2.0 Hz), 4.10 (q, 2H, J = 7.0 Hz), 5.43 (d, 1H, J = 2.0 Hz), 6.70 (d, 1H, J = 8.5 Hz), 6.97 (dt, 1H, J = 7.6 Hz, 1.6 Hz), 7.20 (dd, 1H, J = 8.1 Hz, 1.6 Hz), 7.14-7.21 (m, 2H), 7.41 (t, 1H, J = 7.7 Hz), 7.48 (d, 1H, J = 7.7 Hz), 7.53–7.58 (m, 2H), 7.75 (s, 1H), 8.24 (d, 1H, J = 2.4 Hz); IR (KBr) 1475, 1498, 1604, 2854, 2926, 3393 cm^{-1}; HRMS (ESI, positive) calcd for $C_{30}H_{40}Na_2O_6S$ $(M+Na)^+$ 587.2444; obsd 587.2451.

5.13. Phenyl 2,5-dibromobenzenesulfonate (15)

Chlorosulfonic acid (50 ml) was added to a solution of 1,4-dibromobenzene (50 g, 212 mmol) in chloroform (150 ml) at room temperature. After stirring for 3 h at 80 °C, the reaction mixture was cooled to room temperature and poured into crushed ice, and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give a crude product of sulfonyl chloride. This residual crude product was dissolved in CH_2Cl_2 (200 ml), to which were added PhOH (16.4 g, 174 mmol) and Et_3N (29 ml, 209 mmol), and the mixture was stirred for 1 h at 0 °C. After the addition of satd $NaHCO_3$ (20 ml), the resulting mixture was poured into water and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give the crude product. Recrystallization from MeOH gave the title compound (54.1 g, 65%) as a white crystalline solid. Mp 104–106 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, 2H, J = 7.8 Hz), 7.27–7.36 (m, 3H), 7.59 (dd, 1H, J = 2.9 Hz, 8.8 Hz), 7.69 (d, 1H, J = 8.8 Hz), 8.08 (d, 1H, J = 2.9 Hz); IR (KBr) 1485, 1446, 1387, 1197, 1023 cm^{-1}; HRMS (FAB, positive) calcd for $C_{12}H_8Br_2O_3S$ $(M)^+$ 398.8561; obsd 398.8566.

5.14. Phenyl 5-bromo-2-[(4-hydroxyphenyl)thio]benzenesulfonate (16)

N,*N*-diisopropylethylamine (57.0 ml, 336 mmol) and 4-hydroxythiophenol (21.2 g, 168 mmol) were added to a solution of compound **15** (44.0 g, 112 mmol) in DMF (100 ml). After stirring for 6 h at 80 °C, satd $NaHCO_3$ (20 ml) was added to the reaction mixture. The resulting mixture was poured into water and extracted with ether. The combined organic layer was washed with 3 M aqueous HCl (200 ml) and brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give the crude product, which was purified by silica gel column

chromatography. Elution with EtOAc/hexane (1:4–2:3) afforded the title compound (39.1 g, 77%) as a pale yellow crystalline solid. Mp 148–150 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (brs, 1H), 6.76 (d, 1H, J = 8.8 Hz), 6.95 (d, 2H, J = 8.8 Hz), 7.20 (d, 2H, J = 7.8 Hz), 7.29 (t, 1H, J = 7.8 Hz), 7.36 (t, 2H, J = 7.8 Hz), 7.42 (dd, 1H, J = 2.9 Hz, 8.8 Hz), 7.45 (d, 2H, J = 8.8 Hz), 7.96 (d, 1H, J = 2.9 Hz); IR (KBr) 3472, 1599, 1584, 1495, 1487, 1443, 1379, 1361 cm^{-1}; HRMS (FAB, positive) calcd for $C_{18}H_{13}BrO_4S_2$ $(M)^+$ 453.9439; obsd 453.9436.

5.15. Phenyl 5-bromo-2-[(4-butoxyphenyl)thio]benzenesulfonate (17d)

1-Bromobutane (3.2 ml, 30 mmol) and DBU (4.6 ml, 30 mmol) were added to a solution of compound **16** (8.7 g, 20.0 mmol) in DMF (20 ml). After stirring for 4 h at 60 °C, the reaction mixture was cooled to room temperature and poured into water (50 ml) followed by extraction with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give the crude product. Recrystallization from AcOEt/hexane (1:9) gave the title compound (8.1 g, 82%) as a white crystalline solid. Mp 80–82 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 6.8 Hz), 1.51 (sextet, 2H, J = 6.8 Hz), 1.80 (quintet, 2H, J = 6.8 Hz), 4.01 (t, 2H, J = 6.8 Hz), 6.75 (d, 1H, J = 8.8 Hz), 6.98 (d, 2H, J = 8.8 Hz), 7.20 (d, 2H, J = 7.8 Hz), 7.28 (t, 1H, J = 6.8 Hz), 7.35 (t, 2H, J = 8.8 Hz), 7.40 (dd, 1H, J = 2.0 Hz, 8.8 Hz), 7.47 (d, 2H, J = 8.8 Hz), 7.96 (d, 1H, J = 2.0 Hz); IR (KBr) 1592, 1489, 1443, 1384, 1249 cm^{-1}; HRMS (FAB, positive) calcd for $C_{22}H_{21}BrO_4S_2$ $(M)^+$ 492.0065; obsd 492.0054.

5.16. Phenyl 5-bromo-2-[(4-methoxyphenyl)thio]benzenesulfonate (17a)

The title compound was synthesized in the same manner as the general procedure for compound **17d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.75 (d, 1H, J = 8.6 Hz), 7.00 (dd, 2H, J = 8.8 Hz, 2.1 Hz), 7.19–7.24 (m, 2H), 7.27–7.38 (m, 3H), 7.41 (dd, 1H, J = 8.6 Hz, 2.2 Hz), 7.50 (dd, 2H, J = 8.8 Hz, 2.1 Hz), 7.97 (d, 1H, J = 2.2 Hz); IR (thin film) 1588, 1492, 1443, 1377 cm^{-1}; MS (FAB) m/z: 473 $(M+Na)^+$.

5.17. Phenyl 5-bromo-2-[(4-ethoxyphenyl)thio]benzenesulfonate (17b)

The title compound was synthesized in the same manner as the general procedure for compound **17d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, 3H, J = 7.0 Hz), 4.08 (q, 2H, J = 7.0 Hz), 6.73 (d, 1H, J = 8.6 Hz), 6.98 (d, 2H, J = 8.6 Hz), 7.20 (d, 2H, J = 8.6 Hz), 7.26–7.43 (m, 4H), 7.48 (d, 2H, J = 8.6 Hz), 7.95 (d, 1H, J = 2.0 Hz).

5.18. Phenyl 5-bromo-2-[(4-propoxyphenyl)thio]benzenesulfonate (17c)

The title compound was synthesized in the same manner as the general procedure for compound **17d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, 3H, J = 7.4 Hz), 1.80–1.90 (m, 2H), 3.98 (t, 2H, J = 6.5 Hz), 6.75 (d, 1H, J = 8.6 Hz), 6.99 (dd, 2H, J = 2.1 Hz, 8.8 Hz), 7.18–7.23 (m, 2H), 7.26–7.32 (m, 1H), 7.33–7.38 (m, 2H), 7.40 (dd, 1H, J = 2.2 Hz, 8.6 Hz), 7.48 (dd, 2H, J = 2.1 Hz, 8.8 Hz), 7.96 (d, 1H, J = 2.2 Hz); IR (thin film) 1592, 1489, 1443, 1384, 1250 cm^{-1}; HRMS (ESI, positive) calcd for $C_{21}H_{19}O_4BrS_2Na$ $(M+Na)^+$ 500.9806; obsd 500.9781.

5.19. Phenyl 5-bromo-2-[(4-hexyloxyphenyl)thio]benzenesulfonate (17e)

The title compound was synthesized in the same manner as the general procedure for compound **17d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.1 Hz), 1.35–1.52 (m, 4H), 1.78–1.87 (m, 2H), 4.01 (t, 2H, J = 6.6 Hz), 6.75 (d, 1H, J = 8.6 Hz), 6.99 (dd, 2H, J = 2.1 Hz, 8.8 Hz), 7.18–7.23 (m, 2H), 7.26–7.32 (m, 1H), 7.33–7.38 (m, 2H), 7.40 (dd, 1H, J = 2.2 Hz, 8.6 Hz), 7.48 (dd, 2H, J = 2.1 Hz, 8.8 Hz), 7.96 (d, 1H, J = 2.2 Hz); IR (KBr) 1594, 1489, 1442, 1383, 1252 cm^{-1}; HRMS (ESI, positive) calcd for $C_{23}H_{23}O_4BrS_2Na$ $(M+Na)^+$ 529.0119; obsd 529.0155.

5.20. Phenyl 5-bromo-2-[(4-octyloxyphenyl)thio]benzenesulfonate (17f)

The title compound was synthesized in the same manner as the general procedure for compound **17d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 6.9 Hz), 1.24–1.41 (m, 8H), 1.44–1.53 (m, 2H), 1.77–1.86 (m, 2H), 4.00 (t, 2H, J = 6.5 Hz), 6.75 (d, 1H, J = 8.6 Hz), 6.99 (dd, 2H, J = 8.8 Hz, 2.1 Hz), 7.18–7.23 (m, 2H), 7.26–7.32 (m, 1H), 7.33–7.38 (m, 2H), 7.40 (dd, 1H, J = 8.8 Hz, 2.1 Hz), 7.48 (dd, 2H, J = 8.6 Hz, 2.2 Hz), 7.96 (d, 1H, J = 2.2 Hz); IR (thin film) 2854, 1592, 1490, 1442, 1379 cm^{-1}; MS (FAB) m/z: 548 $(M)^+$.

5.21. Phenyl 4-[(4-butoxyphenyl)thio]-2′-formylbiphenyl-3-sulfonate (18d)

4.6 M aqueous solution of K_2CO_3 (10 ml, 46 mmol) was added to a solution of compound **17d** (7.6 g, 15.4 mmol), 2-formylbenzeneboric acid (2.8 g, 18.5 mmol), and $Pd(PPh_3)_4$ (0.80 g, 0.7 mmol) in dimethoxyethane (20 ml). After stirring for 5 h at 60 °C, the reaction mixture was poured into water (30 ml) and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give the crude product, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (1:9) afforded the title compound (6.8 g, 90%) as a white crystalline solid. Mp 95–97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 6.8 Hz), 1.51 (sextet, 2H, J = 6.8 Hz), 1.80 (quintet, 2H, J = 6.8 Hz), 4.00 (q, 2H, J = 6.8 Hz), 6.98–7.01 (m, 3H), 7.18–7.29 (m, 3H), 7.34 (t, 2H, J = 6.8 Hz), 7.52–7.60 (m, 4H), 7.73 (d, 1H, J = 7.8 Hz), 7.87 (d, 1H, J = 7.8 Hz), 7.96 (s, 1H), 8.10 (s, 1H), 10.05 (s, 1H); IR (KBr) 1700, 1594, 1489, 1250, 1194, 1174, 1145 cm^{-1}; HRMS (FAB, positive) calcd for $C_{27}H_{22}O_5S_2$ $(M)^+$ 490.0909; obsd 490.0897.

5.22. Phenyl 4-[(4-methoxyphenyl)thio]-2′-formylbiphenyl-3-sulfonate (18a)

The title compound was synthesized in the same manner as the general procedure for compound **18d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.75 (d, 1H, J = 8.6 Hz), 7.00 (dd, 2H, J = 8.8 Hz, 2.1 Hz), 7.19–7.24 (m, 2H), 7.27–7.38 (m, 3H), 7.41 (dd, 1H, J = 8.6 Hz, 2.2 Hz), 7.50 (dd, 2H, J = 8.8 Hz, 2.1 Hz), 7.97 (d, 1H, J = 2.2 Hz), 8.08 (s, 1H), 10.04 (s, 1H).

5.23. Phenyl 4-[(4-ethoxyphenyl)thio]-2′-formylbiphenyl-3-sulfonate (18b)

The title compound was synthesized in the same manner as the general procedure for compound **18d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (t, 3H, J = 6.8 Hz), 4.11 (q, 2H, J = 6.8 Hz), 6.98–7.03 (m, 3H), 7.22–7.29 (m, 3H), 7.34 (t, 2H, J = 6.8 Hz), 7.52–7.60 (m, 4H), 7.71 (d, 1H, J = 7.8 Hz), 7.85 (d, 1H, J = 7.8 Hz), 7.95 (s, 1H), 8.08 (s, 1H), 10.04 (s, 1H); IR (KBr) 1700, 1594, 1489, 1250, 1194, 1174, 1145 cm^{-1}.

5.24. Phenyl 4-[(4-propoxyphenyl)thio]-2′-formylbiphenyl-3-sulfonate (18c)

The title compound was synthesized in the same manner as the general procedure for compound **18d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, 3H, J = 7.4 Hz), 1.80–1.90 (m, 2H), 3.98 (t, 2H, J = 6.5 Hz), 6.98–7.03 (m, 3H), 7.22–7.29 (m, 3H), 7.34 (t, 2H, J = 6.8 Hz), 7.52–7.60 (m, 4H), 7.71 (d, 1H, J = 7.8 Hz), 7.85 (d, 1H, J = 7.8 Hz), 7.95 (s, 1H), 8.08 (s, 1H), 10.04 (s, 1H).

5.25. Phenyl 4-[(4-hexyloxyphenyl)thio]-2′-formylbiphenyl-3-sulfonate (18e)

The title compound was synthesized in the same manner as the general procedure for compound **18d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.1 Hz), 1.35–1.52 (m, 4H), 1.78–1.87 (m, 2H), 4.01 (t, 2H, J = 6.6 Hz), 7.00 (dd, 2H, J = 8.8 Hz, 2.1 Hz), 7.19–7.24 (m, 2H), 7.27–7.38 (m, 3H), 7.41 (dd, 1H, J = 8.6 Hz, 2.2 Hz), 7.50 (dd, 2H, J = 8.8 Hz, 2.1 Hz), 7.97 (d, 1H, J = 2.2 Hz), 8.08 (s, 1H), 10.04 (s, 1H).

5.26. Phenyl 4-[(4-octyloxyphenyl)thio]-2′-formylbiphenyl-3-sulfonate (18f)

The title compound was synthesized in the same manner as the general procedure for compound **18d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 6.9 Hz), 1.24–1.41 (m, 8H), 1.44–1.53 (m, 2H), 1.77–1.86 (m, 2H), 4.00 (t, 2H, J = 6.5 Hz), 7.00 (dd, 2H, J = 8.8 Hz, 2.1 Hz), 7.19–7.24 (m, 2H), 7.25–7.36 (m, 3H), 7.42 (dd, 1H, J = 8.6 Hz, 2.2 Hz), 7.48 (dd, 2H, J = 8.8 Hz, 2.1 Hz), 7.99 (d, 1H, J = 2.2 Hz), 8.08 (s, 1H), 10.03 (s, 1H).

5.27. Phenyl 4-[(4-butoxyphenyl)thio]-2′-(1-hydroxytridec-2-yn-1-yl)biphenyl-3-sulfonate (19d)

1.6 M solution of *n*-butyllithium in hexane (19.0 ml, 30 mmol) was added to a solution of 1-dodecyne (7.7 ml, 36 mmol) in THF (40 ml) at −45 °C. After stirring for 10 min, a solution of compound **18d** (9.8 g, 20 mmol) in THF (10 ml) was added to the reaction mixture. After stirring for 1 h, satd NH_4Cl (10 ml) was added to the reaction mixture. The resulting mixture was poured into water and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give the crude product, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (1:3–1:1) afforded the title compound (11.4 g, 83%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 1.00 (t, 3H, J = 7.8 Hz), 1.20–1.38 (m, 14H), 1.45–1.55 (m, 4H), 1.81 (quintet, 2H, J = 8.8 Hz), 2.20 (dt, 2H, J = 2.0 Hz, 6.8 Hz), 4.03 (t, 2H, J = 6.8 Hz), 5.01 (s, 1H), 6.93 (d, 1H, J = 8.8 Hz), 7.01 (d, 2H, J = 8.8 Hz), 7.06 (d, 1H, J = 7.8 Hz), 7.21 (d, 2H, J = 7.8 Hz), 7.25–7.42 (m, 6H), 7.55 (d, 1H, J = 7.8 Hz), 7.80 (d, 1H, J = 7.8 Hz), 7.91 (d, 1H, J = 2.0 Hz); IR (liquid film) 3535, 1593, 1489, 1458, 1388, 1367, 1248 cm^{-1}; HRMS (ESI, positive) calcd for $C_{41}H_{48}NaO_5S_2$ $(M+Na)^+$ 707.2841; obsd 707.2836.

5.28. Phenyl 4-[(4-methoxyphenyl)thio]-2′-(1-hydroxytridec-2-yn-1-yl)biphenyl-3-sulfonate (19a)

The title compound was synthesized in the same manner as the general procedure for compound **19d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 6.9 Hz), 1.27 (br s, 12H), 1.32–1.39 (m, 2H), 1.46–1.55 (m, 2H), 1.88 (d, 1H, J = 5.2 Hz), 2.22 (dt, 2H, J = 7.2 Hz, 1.9 Hz), 3.90 (s, 3H), 5.00–5.03 (m, 1H), 6.94 (d, 1H, J = 8.1 Hz), 7.04 (dd, 2H, J = 8.9 Hz, 2.1 Hz), 7.09 (dd, 1H, J = 7.6 Hz, 1.2 Hz), 7.22–7.25 (m, 2H), 7.27–7.44 (m, 6H), 7.59 (dd, 2H, J = 2.1 Hz, 8.9 Hz), 7.82 (dd, 1H, J = 7.8 Hz, 1.3 Hz), 7.93 (d, 1H, J = 2.0 Hz); IR (thin film) 2925, 2854, 1591, 1493, 1458, 1387 cm^{-1}; MS (ESI) m/z: 665 $(M+Na)^+$.

5.29. Phenyl 4-[(4-ethoxyphenyl)thio]-2′-(1-hydroxytridec-2-yn-1-yl)biphenyl-3-sulfonate (19b)

The title compound was synthesized in the same manner as the general procedure for compound **19d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 1.47 (t, 3H, J = 7.8 Hz), 1.20–1.38 (m, 14H), 1.81 (quintet, 2H, J = 8.8 Hz), 2.20 (dt, 2H, J = 2.0 Hz, 6.8 Hz), 4.08 (t, 2H, J = 6.8 Hz), 5.01 (s, 1H), 6.93 (d, 1H, J = 8.8 Hz), 7.01 (d, 2H, J = 8.8 Hz), 7.06 (d, 1H, J = 7.8 Hz), 7.21 (d, 2H, J = 7.8 Hz), 7.25–7.42 (m, 6H), 7.55 (d, 1H, J = 7.8 Hz), 7.80 (d, 1H, J = 7.8 Hz), 7.91 (d, 1H, J = 2.0 Hz).

5.30. Phenyl 4-[(4-propoxyphenyl)thio]-2′-(1-hydroxytridec-2-yn-1-yl)biphenyl-3-sulfonate (19c)

The title compound was synthesized in the same manner as the general procedure for compound **19d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.9 Hz), 1.07 (t, 3H, J = 7.4 Hz), 1.25 (brs, 12H), 1.30–1.38 (m, 2H), 1.43–1.52 (m, 2H), 1.81–1.92 (m, 3H), 2.20 (td, 2H, J = 1.9 Hz, 7.1 Hz), 3.99 (t, 2H, J = 6.5 Hz), 4.98–5.02

(m, 1H), 6.93 (d, 1H, $J = 8.3$ Hz), 7.02 (dd, 2H, $J = 2.0$ Hz, 8.8 Hz), 7.08 (dd, 1H, $J = 1.2$ Hz, 7.6 Hz), 7.20–7.25 (m, 2H), 7.27–7.44 (m, 6H), 7.56 (dd, 2H, $J = 2.0$ Hz, 8.8 Hz), 7.81 (dd, 1H, $J = 1.1$ Hz, 7.8 Hz), 7.91 (d, 1H, $J = 1.9$ Hz); IR (thin film) 3530, 2926, 1592, 1489, 1458, 1248 cm^{-1}; HRMS (ESI, positive) calcd for $C_{40}H_{46}O_5S_2Na$ $(M+Na)^+$ 693.2684; obsd 693.2707.

5.31. Phenyl 4-[(4-hexyloxyphenyl)thio]-2′-(1-hydroxytridec-2-yn-1-yl)biphenyl-3-sulfonate (19e)

The title compound was synthesized in the same manner as the general procedure for compound **19d**. ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J = 6.6$ Hz), 0.95 (t, 3H, $J = 7.1$ Hz), 1.25 (brs, 12H), 1.30–1.37 (m, 2H), 1.37–1.53 (m, 6H), 1.79–1.87 (m, 2H), 1.88 (d, 1H, $J = 5.2$ Hz), 2.20 (dt, 2H, $J = 2.1$ Hz, 7.2 Hz), 4.02 (t, 2H, $J = 6.5$ Hz), 4.98–5.03 (m, 1H), 6.93 (d, 1H, $J = 8.3$ Hz), 7.01 (dd, 2H, $J = 2.1$ Hz, 8.8 Hz), 7.08 (dd, 1H, $J = 1.3$ Hz, 7.6 Hz), 7.21–7.25 (m, 2H), 7.27–7.44 (m, 6H), 7.56 (dd, 2H, $J = 2.1$ Hz, 8.8 Hz), 7.80 (dd, 1H, $J = 1.2$ Hz, 7.8 Hz), 7.91 (d, 1H, $J = 2.0$ Hz); IR (thin film) 3536, 2926, 2855, 1593, 1489, 1458 cm^{-1}; HRMS (ESI, positive) calcd for $C_{45}H_{56}O_5S_2Na$ $(M+Na)^+$ 763.3466; obsd 763.3456.

5.32. Phenyl 4-[(4-octyloxyphenyl)thio]-2′-(1-hydroxytridec-2-yn-1-yl)biphenyl-3-sulfonate (19f)

The title compound was synthesized in the same manner as the general procedure for compound **19d**. ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, $J = 6.9$ Hz), 1.27 (br s, 12H), 1.32–1.39 (m, 2H), 1.46–1.55 (m, 2H), 1.88 (d, 1H, $J = 5.2$ Hz), 2.22 (dt, 2H, $J = 7.2$ Hz, 1.9 Hz), 3.90 (s, 3H), 5.00–5.03 (m, 1H), 6.94 (d, 1H, $J = 8.1$ Hz), 7.04 (dd, 2H, $J = 8.9$ Hz, 2.1 Hz), 7.09 (dd, 1H, $J = 7.6$ Hz, 1.2 Hz), 7.22–7.25 (m, 2H), 7.27–7.44 (m, 6H), 7.59 (dd, 2H, $J = 2.1$ Hz, 8.9 Hz), 7.82 (dd, 1H, $J = 7.8$ Hz, 1.3 Hz), 7.93 (d, 1H, $J = 2.0$ Hz); IR (thin film) 2925, 2854, 1591, 1493, 1458, 1387 cm^{-1}; MS (ESI, positive) *m/z*: 665 $(M+Na)^+$.

5.33. Sodium 4-[(4-butoxyphenyl)thio]-2′-(1-hydroxytridec-2-yn-1-yl)biphenyl-3-sulfonate (20d)

NaOH (0.12 g, 2.9 mmol) was added to a solution of compound **19d** (0.25 g, 0.36 mmol) in a mixed solvent of dioxane (1 ml) and water (0.3 ml). After stirring for 8 h at 90 °C, the resulting mixture was purified by silica gel column chromatography. Elution with $MeOH/CH_2Cl_2$ (1:4) afforded the title compound (0.19 g, 84%) as an amorphous solid. ^1H NMR (500 MHz, CD_3OD) δ 0.89 (t, 3H, $J = 7.3$H), 0.99 (t, 3H, $J = 7.3$ Hz), 1.21–1.39 (m, 14H), 1.40–1.57 (m, 4H), 1.78 (quintet, 2H, $J = 6.6$ Hz), 2.18 (dt, 2H, $J = 1.5$ Hz, 6.6 Hz), 4.02 (t, 2H, $J = 6.6$ Hz), 5.29 (s, 1H), 6.82 (d, 1H, $J = 8.1$ Hz), 7.00 (d, 2H, $J = 8.8$ Hz), 7.18 (d, 1H, $J = 7.3$ Hz), 7.22 (dd, 1H, $J = 2.2$ Hz, 8.1 Hz), 7.32 (t, 1H, $J = 6.6$ Hz), 7.38 (t, 1H, $J = 7.3$ Hz), 7.54 (d, 2H, $J = 8.1$ Hz), 7.78 (d, 1H, $J = 8.1$ Hz), 7.99 (d, 1H, $J = 2.2$ Hz); IR (KBr) 3386, 1593, 1494, 1458, 1243 cm^{-1}; HRMS (ESI, positive) calcd for $C_{35}H_{43}Na_2O_5S_2$ $(M+Na)^+$ 653.2347; obsd 653.2345.

5.34. Sodium 2′-(1-hydroxytridec-2-yn-1-yl)-4-[(4-methoxyphenyl)thio]biphenyl-3-sulfonate (20a)

The title compound (50 mg, 65% from **19a**) was synthesized in the same manner as the general procedure for **20d**. ^1H NMR (400 MHz, CD_3OD) δ 0.89 (t, 3H, $J = 6.9$ Hz), 1.20–1.33 (m, 12H), 1.30–1.38 (m, 2H), 1.41–1.50 (m, 2H), 2.19 (td, 2H, $J = 6.9$ Hz, 2.0 Hz), 3.85 (s, 3H), 5.29 (t, 1H, $J = 2.1$ Hz), 6.82 (d, 1H, $J = 8.2$ Hz), 7.02 (dd, 2H, $J = 8.8$ Hz, 2.1 Hz), 7.19 (dd, 1H, $J = 7.6$ Hz, 1.4 Hz), 7.22 (dd, 1H, $J = 8.2$ Hz, 2.1 Hz), 7.32 (td, 1H, $J = 7.6$ Hz, 1.4 Hz), 7.38 (td, 1H, $J = 7.6$ Hz, 1.4 Hz), 7.57 (dd, 2H, $J = 8.8$ Hz, 2.1 Hz), 7.79 (dd, 1H, $J = 7.6$ Hz, 1.4 Hz), 7.99 (d, 1H, $J = 2.1$ Hz); IR (KBr) 1444, 1458, 1495, 1592, 2854, 2926, 3423 cm^{-1}; HRMS (ESI, positive) calcd for $C_{32}H_{37}Na_2O_5S_2$ $(M+Na)^+$ 611.1878; obsd 611.1871.

5.35. Sodium 4-[(4-ethoxyphenyl)thio]-2′-(1-hydroxytridec-2-yn-1-yl)biphenyl-3-sulfonate (20b)

The title compound (16 mg, 38% from **19b**) was synthesized in the same manner as the general procedure for **20d**. ^1H NMR (500 MHz, CD_3OD) δ 0.88 (t, 3H, $J = 7.8$ Hz), 1.20–1.33 (m, 12H), 1.37–1.44 (m, 4H), 1.51 (quintet, 2H, $J = 7.8$ Hz), 2.26 (dt, 2H, $J = 2.0$ Hz, 6.8 Hz), 4.08 (q, 2H, $J = 6.8$ Hz), 5.41 (s, 1H), 6.87 (d, 1H, $J = 8.8$ Hz), 6.99 (d, 2H, $J = 8.8$ Hz), 7.38–7.49 (m, 3H), 7.53 (d, 2H, $J = 8.8$ Hz), 7.74 (s, 1H), 8.24 (d, 1H, $J = 2.0$ Hz); IR (KBr) 1197, 1243, 1459, 1494, 1594, 3412 cm^{-1}; HRMS (ESI, positive) calcd for $C_{33}H_{39}Na_2O_5S_2$ $(M+Na)^+$ 625.2034; obsd 625.2050.

5.36. Sodium 2′-(1-hydroxytridec-2-yn-1-yl)-4-[(4-propoxyphenyl)thio]biphenyl-3-sulfonate (20c)

The title compound (35 mg, 60% from **19c**) was synthesized in the same manner as the general procedure for **20d**. ^1H NMR (400 MHz, CD_3OD) δ 0.89 (t, 3H, $J = 6.9$ Hz), 1.06 (t, 3H, $J = 7.4$ Hz), 1.25 (brs, 12H), 1.31–1.39 (m, 2H), 1.40–1.50 (m, 2H), 1.77–1.88 (m, 2H), 2.19 (td, 2H, $J = 1.9$ Hz, 6.9 Hz), 3.99 (t, 2H, $J = 6.5$ Hz), 5.29 (t, 1H, $J = 1.9$ Hz), 6.83 (d, 1H, $J = 8.2$ Hz), 7.01 (dd, 2H, $J = 2.0$ Hz, 8.8 Hz), 7.19 (dd, 1H, $J = 1.3$ Hz, 7.5 Hz), 7.22 (dd, 1H, $J = 2.0$ Hz, 8.2 Hz), 7.32 (td, 1H, $J = 1.3$ Hz, 7.5 Hz), 7.38 (td, 1H, $J = 1.3$ Hz, 7.5 Hz), 7.55 (dd, 2H, $J = 2.0$ Hz, 8.8 Hz), 7.79 (dd, 1H, $J = 1.3$ Hz, 7.5 Hz), 7.99 (d, 1H, $J = 2.0$ Hz); IR (KBr) 3368, 1593, 1494, 1458, 1241 cm^{-1}; HRMS (ESI, negative) calcd for $C_{34}H_{41}O_5S_2$ $(M-Na)^-$ 593.2396; obsd 593.2375.

5.37. Sodium 4-[(4-hexyloxyphenyl)thio]-2′-(1-hydroxytridec-2-yl)biphenyl-3-sulfonate (20e)

The title compound (42 mg, 69% from **19e**) was synthesized in the same manner as the general procedure for **20d**. ^1H NMR (400 MHz, CD_3OD) δ 0.89 (t, 3H, $J = 6.9$ Hz), 0.96 (t, 3H, $J = 7.2$ Hz), 1.25 (brs, 12H), 1.29-1.38 (m, 2H), 1.38–1.53 (m, 6H), 1.76–1.85 (m, 2H), 2.19 (td, 2H, $J = 1.9$ Hz, 6.9 Hz), 4.02 (t, 2H, $J = 6.5$ Hz), 5.29 (t, 1H, $J = 1.9$ Hz), 6.82 (d, 1H, $J = 8.2$ Hz), 7.01 (dd, 2H, $J = 2.1$ Hz, 8.8 Hz), 7.19

(dd, 1H, J = 1.4 Hz, 7.5 Hz), 7.22 (dd, 1H, J = 2.0 Hz, 8.2 Hz), 7.32 (dt, 1H, J = 1.4 Hz, 7.5 Hz), 7.38 (dt, 1H, J = 1.4 Hz, 7.5 Hz), 7.55 (dd, 2H, J = 2.1 Hz, 8.8 Hz), 7.78 (dd, 1H, J = 1.4 Hz, 7.5 Hz), 7.89 (d, 1H, J = 2.0 Hz); IR (KBr) 3411, 1594, 1494, 1458, 1241 cm^{-1}; HRMS (ESI, positive) calcd for $C_{36}H_{45}O_5S_2Na_2$ $(M+Na)^+$ 667.2504; obsd 667.2493.

5.38. Sodium 4-[(4-octyloxyphenyl)thio]-2′-(1-hydroxytridec-2-yn-1-yl)biphenyl-3-sulfonate (20f)

The title compound (54 mg, 79% from **19f**) was synthesized in the same manner as the general procedure for **20d**. ^1H NMR (400 MHz, CD_3OD) δ 0.89 (t, 3H, J = 6.3 Hz), 0.90 (t, 3H, J = 6.3 Hz), 1.25 (brs, 14H), 1.32 (brs, 8H), 1.40–1.54 (m, 4H), 1.75–1.84 (m, 2H), 2.19 (td, 2H, J = 6.9 Hz, 2.0 Hz), 4.02 (t, 2H, J = 6.4 Hz), 5.29 (t, 1H, J = 2.0 Hz), 6.83 (d, 1H, J = 8.2 Hz), 7.00 (dd, 2H, J = 8.8 Hz, 2.1 Hz), 7.19 (dd, 1H, J = 7.5 Hz, 1.4 Hz), 7.22 (d, 1H, J = 8.2 Hz, 2.0 Hz), 7.32 (td, 1H, J = 7.5 Hz, 1.4 Hz), 7.38 (t, 1H, J = 7.5 Hz, 1.4 Hz), 7.55 (dd, 2H, J = 8.8 Hz, 2.1 Hz), 7.85 (dd, 1H, J = 7.5 Hz, 1.4 Hz), 7.99 (d, 1H, J = 2.0 Hz); IR (KBr) 1571, 1593, 1634, 2855, 2926, 3447 cm^{-1}; HRMS (ESI, positive) calcd for $C_{39}H_{51}Na_2O_5S_2$ $(M+Na)^+$ 709.2974; obsd 709.2993.

5.39. Phenyl 4-[(4-butoxyphenyl)thio]-2′-(1-acetoxytridec-2-yn-1-yl)biphenyl-3-sulfonate (21)

Acetic anhydride (0.43 ml, 4.5 mmol) was slowly added to a solution of compound **19d** (1.1 g, 1.5 mmol), 4-dimethylaminopyridine (10 mg, 0.10 mmol), and Et_3N (1.0 ml, 7.5 mmol) in CH_2Cl_2 (3.0 ml) at 0 °C. After stirring for 3 h, satd $NaHCO_3$ (1.0 ml) was added to the reaction mixture. The resulting mixture was poured into water and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give the crude product, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (1:9) afforded the title compound (1.0 g, 95%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 1.00 (t, 3H, J = 7.8 Hz), 1.20–1.33 (m, 14H), 1.45 (quintet, 2H, J = 6.8 Hz), 1.52 (sextet, 2H, J = 7.8 Hz), 1.81 (quintet, 2H, J = 7.8 Hz), 1.97 (s, 3H), 2.15 (dt, 2H, J = 2.0 Hz, 6.8 Hz), 4.03 (t, 2H, J = 6.8 Hz), 6.93 (d, 1H, J = 8.8 Hz), 7.00 (d, 2H, J = 8.8 Hz), 7.07 (d, 1H, J = 6.8 Hz), 7.21–7.43 (m, 6H), 7.54 (d, 2H, J = 8.8 Hz), 7.71 (d, 1H, J = 7.8 Hz), 7.88 (d, 1H, J = 2.0 Hz); IR (liquid film) 1742, 1593, 1489, 1458 cm^{-1}; HRMS (ESI, positive) calcd for $C_{43}H_{50}NaO_6S_2$ $(M+Na)^+$ 749.2946; obsd 749.2943.

5.40. Phenyl 4-[(4-butoxyphenyl)thio]-2′-tridec-2-yn-1-ylbiphenyl-3-sulfonate (22a)

Triethylsilane (20 μl, 0.12 mmol) and trifluoroacetic acid (13 μl, 0.16 mmol) were added to a solution of compound **21** (56 mg, 0.081 mmol) in CH_2Cl_2 (0.5 ml) at 0 °C. After stirring for 4 h, the reaction mixture was added satd $NaHCO_3$ (0.2 ml). The resulting mixture was poured into water and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give the crude product, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (2:8) afforded the title compound (38 mg, 70%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.8 Hz), 1.00 (t, 3H, J = 7.8 Hz), 1.20–1.38 (m, 14H), 1.42–1.59 (m, 4H), 1.81 (quintet, 2H, J = 6.8 Hz), 2.12–2.18 (m, 2H), 3.15 (s, 2H), 4.03 (t, 2H, J = 5.9 Hz), 6.93 (d, 1H, J = 8.8 Hz), 7.00–7.04 (m, 3H), 7.79 (d, 1H, J = 2.0 Hz); IR (liquid film) 1369, 1388, 1458, 1490, 1593 cm^{-1}; MS (FAB, positive) m/z: 691 $(M+Na)^+$.

5.41. Sodium 4-[(4-butoxyphenyl)thio]-2′-tridec-2-yn-1-ylbiphenyl-3-sulfonate (25a)

NaOH (16 mg, 0.39 mmol) was added to a solution of compound **22a** (33 mg, 0.049 mmol) in a mixed solvent of dioxane (0.30 ml) and H_2O (0.10 ml). After stirring for 24 h at 90 °C, the resulting mixture was purified by silica gel column chromatography. Elution with MeOH/CH_2Cl_2 (1:4) afforded the title compound (10 mg, 33%) as an amorphous solid. ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 6.8 Hz), 1.00 (t, 3H, J = 7.8 Hz), 1.20–1.39 (m, 14H), 1.43 (quintet, 2H, J = 6.8 Hz), 1.52 (sextet, 2H, J = 7.8 Hz), 1.78 (quintet, 2H, J = 6.8 Hz), 2.10–2.16 (m, 1H), 3.38 (s, 1H), 4.02 (t, 2H, J = 6.8 Hz), 6.84 (d, 1H, J = 8.8 Hz), 7.00 (d, 2H, J = 8.8 Hz), 7.11–7.32 (m, 8H), 7.51–7.57 (m, 3H), 7.89 (d, 1H, J = 2.0 Hz); IR (KBr) 1246, 1458, 1494, 1594 cm^{-1}; MS (FAB, positive) m/z: 615 $(M+H)^+$, 637 $(M+Na)^+$.

5.42. Phenyl 4-[(4-butoxyphenyl)thio]-2′-[1-(phenyloxycarbonylamino)tridec-2-yn-1-yl]biphenyl-3-sulfonate (22b)

$BF_3{\cdot}Et_2O$ (0.11 ml, 0.83 mmol) was added to a solution of compound **21** (0.60 g, 0.83 mmol) and phenylcarbamate (0.34 g, 2.5 mmol) in CH_2Cl_2 (1.0 ml) at 0 °C. After stirring for 1 h at room temperature, satd $NaHCO_3$ (1.0 ml) was added to the reaction mixture. The resulting mixture was poured into water and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give the crude product, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (3:17) afforded the title compound (0.60 g, 88%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 0.99 (t, 3H, J = 6.8 Hz), 1.18–1.38 (m, 14H), 1.42–1.57 (m, 4H), 1.80 (quintet, 2H, J = 6.8 Hz), 2.15 (t, 2H, J = 5.9 Hz), 4.01 (t, 2H, J = 5.9 Hz), 5.29 (d, 1H, J = 6.8 Hz), 5.45 (d, 1H, J = 6.8 Hz), 6.92 (d, 1H, J = 8.8 Hz), 6.97 (d, 2H, J = 8.8 Hz), 7.00–7.07 (m, 2H), 7.14–7.44 (m, 8H), 7.51 (d, 2H, J = 8.8 Hz), 7.63 (d, 1H, J = 7.8 Hz), 7.92 (s, 1H); IR (neat) 3391, 1741, 1593, 1488, 1458 cm^{-1}; HRMS (ESI, positive) calcd for $C_{48}H_{53}NNaO_6S_2$ $(M+Na)^+$ 826.3212; obsd 826.3222.

5.43. 2′-(1-Aminotridec-2-yn-1-yl)-4-[(4- butoxyphenyl) thio]biphenyl-3-sulfonate (25b)

NaOH (50 mg, 1.2 mmol) was added to a solution of compound **22b** (50 mg, 0.061 mmol) in a mixed solvent of dioxane (0.30 ml) and H_2O (0.10 ml). After stirring for 8 h at 90 °C, the resulting mixture was purified by silica gel column chromatography. Elution with MeOH/CH_2Cl_2 (1:4) afforded the title compound (12 mg, 40%) as an amorphous solid. ^{1}H NMR (500 MHz, CD_3OD) δ 0.89 (t, 3H, J = 6.8 Hz), 1.00 (t, 3H, J = 6.8 Hz), 1.21–1.38 (m, 14H), 1.42–1.57 (m, 4H), 1.78 (quintet, 2H, J = 6.8 Hz), 2.23 (dt, 2H, J = 2.0 Hz, 6.8 Hz), 4.03 (t, 2H, J = 6.8 Hz), 5.02 (d, 1H, J = 2.0 Hz), 6.86 (d, 1H, J = 8.8 Hz), 7.01 (d, 2H, J = 8.8 Hz), 7.16 (dd, 1H, J = 2.0 Hz, 8.8 Hz), 7.28 (d, 1H, J = 7.8 Hz), 7.43 (t, 1H, J = 7.8 Hz), 7.48 (t, 1H, J = 7.8 Hz), 7.53 (d, 2H, J = 8.8 Hz), 7.76 (d, 1H, J = 7.8 Hz), 7.93 (d, 1H, J = 2.0 Hz); IR (KBr) 3691, 1594, 1494, 1458 cm^{-1}; HRMS (ESI, negative) calcd for $C_{35}H_{44}NO_4S_2$ $(M-Na)^-$ 606.2712; obsd 606.2715.

5.44. Phenyl 4-[(4-butoxyphenyl)thio]-2′-tridec-2-ynoylbiphenyl-3-sulfonate (23)

Dess–Martin periodinane (0.20 g, 0.48 mmol) was added to a solution of compound **19d** (0.16 g, 0.24 mmol) in CH_2Cl_2 at 0 °C. After stirring for 2 h, satd $NaHCO_3$ (0.2 ml) and satd $Na_2S_2O_3$ (0.2 ml) were added to the reaction mixture and stirred for 1 h at room temperature. The resulting mixture was poured into water and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give the crude product, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (1:9) afforded the title compound (0.14 g, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.3 Hz), 1.00 (t, 3H, J = 7.3 Hz), 1.20–1.38 (m, 14H), 1.43-1.57 (m, 4H), 1.76–1.85 (m, 2H), 2.25 (t, 2H, J = 7.3 Hz), 4.02 (t, 2H, J = 6.6 Hz), 6.89 (d, 1H, J = 8.8 Hz), 6.99 (d, 2H, J = 8.8 Hz), 7.15 (d, 1H, J = 8.1 Hz), 7.21–7.29 (m, 4H), 7.33–7.39 (m, 3H), 7.44 (d, 1H, J = 1.5 Hz, 7.3 Hz), 7.46–7.54 (m, 3H), 7.82 (d, 1H, J = 2.2 Hz), 8.01 (dd, 1H, J = 1.5 Hz, 8.8 Hz); IR (liquid film) 1249, 1457, 1489, 1593, 1647, 2210 cm^{-1}; HRMS (ESI, positive) calcd for $C_{41}H_{46}NaO_5S_2$ $(M+Na)^+$ 705.2684; obsd 705.2676.

5.45. Phenyl 4-(4-ethoxyphenoxy)-2′-(1-hydroxy-1-methyltridec-2-yn-1-yl)biphenyl-3-sulfonate (24)

2.0 M solution of methylmagnesiumbromide in ether (0.21 ml, 0.42 mmol) was added to a solution of compound **23** (0.14 g, 0.21 mmol) in THF (1 ml) at −78 °C. After stirring for 2 h, satd NH_4Cl (0.2 ml) was added to the reaction mixture and stirred for 1 h at room temperature. The resulting mixture was poured into water and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give the crude product, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (1:9) afforded the title compound (0.10 g, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 1.00 (t, 3H, J = 6.8 Hz), 1.18–1.33 (m, 18H), 1.34–1.43 (m, 2H), 1.46–1.55 (m, 4H), 1.81 (quintet, 2H, J = 7.8 Hz), 2.02 (t, 2H, J = 7.0 Hz), 4.02 (t, 2H, J = 6.6 Hz), 6.87 (d, 1H, J = 6.6 Hz), 6.90 (d, 1H, J = 7.3 Hz), 7.00 (d, 2H, J = 8.1 Hz), 7.22–7.38 (m, 8H), 7.54 (d, 2H, J = 8.1 Hz), 7.78 (d, 1H, J = 8.1 Hz), 7.87 (d, 1H, J = 2.0 Hz).

5.46. Sodium 4-(4-ethoxyphenoxy)-2′-(1-hydroxy-1-methyl tridec-2-yn-1-yl)biphenyl-3-sulfonate (25c)

NaOH (16 mg, 0.39 mmol) was added to a solution of compound **24** (36 mg, 0.050 mmol) in a mixed solvent of dioxane (0.30 ml) and H_2O (0.10 ml). After stirring for 6 h at 90 °C, the resulting mixture was purified by silica gel column chromatography. Elution with MeOH/CH_2Cl_2 (1:4) afforded the title compound (16 mg, 47%) as an amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, 3H, J = 6.8 Hz), 0.95 (t, 3H, J = 6.8 Hz), 1.15–1.33 (m, 18H), 1.48 (sextet, 2H, J = 6.8 Hz), 1.70–1.78 (m, 2H), 1.96 (t, 2H, J = 7.0 Hz), 3.98 (t, 2H, J = 6.8 Hz), 6.71 (d, 1H, J = 8.1 Hz), 6.93–6.98 (m, 4H), 7.12 (dt, 1H, J = 8.2 Hz, 2.0 Hz), 7.20 (t, 1H, J = 8.2 Hz), 7.28 (t, 1H, J = 8.2 Hz), 7.50 (d, 2H, J = 8.8 Hz), 7.80 (d, 1H, J = 6.6 Hz), 7.85 (d, 1H, J = 2.0 Hz).

5.47. 2-(Undec-10-ynyloxy)tetrahydro-2*H*-pyrane (27)

p-TsOH (26 mg, 0.15 mmol) was added to a solution of 10-undecyn-1-ol (0.50 g, 3.0 mmol) and 3,4-dihydro-2*H*-pyran (0.41 ml, 4.5 mmol) in CH_2Cl_2 at 0 °C. After stirring for 30 min, satd $NaHCO_3$ (1.0 ml) was added to the reaction mixture. The resulting mixture was poured into water and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give the crude product, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (1:20) afforded the title compound (0.69 g, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26–1.42 (brs, 10H), 1.49–1.54 (m, 4H), 1.55–1.61 (m, 4H), 1.69–1.75 (m, 1H), 1.80–1.86 (m, 1H), 1.94 (d, 1H, J = 2.6 Hz), 2.18 (dt, 2H, J = 2.9 Hz, 10.3 Hz), 3.35–3.41 (m, 1H), 3.48–3.53 (m, 1H), 3.70–3.76 (m, 1H), 3.85–3.90 (m, 1H), 4.58 (t, 1H, J = 2.9 Hz); IR (liquid film) 3312, 2933, 2857, 1033 cm^{-1}; HRMS (EI, positive) calcd for $C_{16}H_{28}O_2$ $(M-H)^+$ 251.2011; obsd 251.2017.

5.48. 2-[[3-(Prop-2-ynyloxy)propyl]oxy]tetrahydro-2*H*-pyran (29a)

55 wt% of NaH (84 mg, 4.0 mmol) was added to a solution of propargylalcohol (61 ml, 1.1 mmol) and 2-[(3-bromopropyl)oxy]tetrahydro-2*H*-pyran (0.18 g, 0.70 mmol) in DMF at 0 °C. After stirring for 3 h, satd NH_4Cl (1.0 ml) was added to the reaction mixture. The resulting mixture was poured into water and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate

was evaporated in vacuo to give the crude product, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (1:20) afforded the title compound (0.10 g, 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46–1.63 (m, 4H), 1.65–1.75 (m, 1H), 1.77–1.94 (m, 3H), 2.41 (t, 1H, J = 2.4 Hz), 3.45–3.54 (m, 2H), 3.58–3.67 (m, 2H), 3.89–3.90 (m, 2H), 4.14 (d, 2H, J = 2.4 Hz), 4.59 (dd, 1H, J = 4.4 Hz, 2.8 Hz); IR (thin film) 3291, 3261, 2944, 2870, 2115, 1442 cm^{-1}; MS (EI, positive) m/z: 197 $(M-H)^+$.

5.49. 2-[[5-(Prop-2-ynyloxy)pentyl]oxy]tetrahydro-2*H*-pyran (29b)

The title compound was synthesized in the same manner as the general procedure for **29a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40–1.76 (m, 11H), 1.78–1.87 (m, 1H), 2.41 (t, 1H, J = 2.4 Hz), 3.39 (td, 1H, J = 6.6 Hz, 9.6 Hz), 3.47–3.53 (m, 1H), 3.52 (t, 2H, J = 6.6 Hz), 4.13 (d, 2H, J = 2.4 Hz), 4.57 (dd, 1H, J = 2.8 Hz, 4.4 Hz); IR (thin film) 3261, 2941, 2867, 1354 cm^{-1}; MS (ESI, positive) m/z: 249 $(M+Na)^+$.

5.50. 2-[[7-(Prop-2-ynyloxy)heptyl]oxy]tetrahydro-2*H*-pyran (29c)

The title compound was synthesized in the same manner as the general procedure for **29a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32–1.42 (m, 6H), 1.48–1.65 (m, 8H), 1.68–1.75 (m, 1H), 1.78–1.87 (m, 1H), 2.41 (t, 1H, J = 2.4 Hz), 3.38 (td, 1H, J = 6.6 Hz, 9.6 Hz), 3.47–3.53 (m, 1H), 3.51 (t, 2H, J = 6.6 Hz), 3.73 (td, 1H, J = 6.9 Hz, 9.6 Hz), 3.74–3.89 (m, 1H), 4.13 (d, 2H, J = 2.4 Hz), 4.57 (dd, 1H, J = 3.0 Hz, 4.1 Hz).

5.51. 2-[[9-(Prop-2-ynyloxy)nonyl]oxy]tetrahydro-2*H*-pyran (29d)

The title compound was synthesized in the same manner as the general procedure for **29a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (brs, 10H), 1.48–1.63 (m, 8H), 1.67–1.76 (m, 1H), 1.79–1.88 (m, 1H), 2.41 (t, 1H, J = 2.4 Hz), 3.38 (td, 1H, J = 6.7 Hz, 9.6 Hz), 3.46–3.53 (m, 1H), 3.51 (t, 2H, J = 6.6 Hz), 3.73 (td, 1H, J = 6.9 Hz, 9.6 Hz), 3.84–3.90 (m, 1H), 4.13 (d, 2H, J = 2.4 Hz), 4.57 (dd, 1H, J = 2.8 Hz, 4.4 Hz); IR (liquid film) 3310, 2934, 2856, 1354 cm^{-1}; MS (EI, positive) m/z: 281 $(M-H)^+$.

5.52. 2-[[11-(Prop-2-ynyloxy)undecyl]oxy]tetrahydro-2*H*-pyran (29e)

The title compound was synthesized in the same manner as the general procedure for **29a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (br s, 14H), 1.48–1.63 (m, 8H), 1.67–1.75 (m, 1H), 1.78–1.88 (m, 1H), 2.41 (t, 1H, J = 2.4 Hz), 3.38 (td, 1H, J = 6.7 Hz, 9.6 Hz), 3.46–3.53 (m, 1H), 3.51 (t, 2H, J = 6.7 Hz), 3.73 (td, 1H, J = 6.9 Hz, 9.6 Hz), 3.84–3.91 (m, 1H), 4.13 (d, 2H, J = 2.4 Hz), 4.58 (dd, 1H, J = 2.8 Hz, 4.3 Hz); IR (liquid film) 3311, 2929, 1354 cm^{-1}; MS (ESI, positive) m/z: 309 $(M-H)^+$.

5.53. Phenyl 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-12-(tetrahydro-2*H*-pyran-2- yloxy)dodec-2-yn-1-yl]biphenyl -3-sulfonate (30)

1.6 M Solution of *n*-BuLi in hexane (0.23 ml, 0.36 mmol) was added to a solution of compound **27** (0.10 g, 0.40 mmol) in THF (1.0 ml) at −78 °C. After stirring for 10 min, a solution of aldehyde **18d** (0.10 g, 0.40 mmol) in THF (1.0 ml) was added to the reaction mixture via cannula. After stirring for 1 h, satd NH_4Cl (1.0 ml) was added to the reaction mixture. The resulting mixture was poured into water and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give the crude product, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (1:3) afforded the title compound (0.10 g, 66%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.3 Hz), 1.24–1.36 (brs, 10H), 1.45–1.60 (m, 10H), 1.68-1.74 (m, 1H), 1.78–1.85 (m, 3H), 1.99 (d, 1H, J = 5.1 Hz), 2.20 (dt, 2H, J = 2.2 Hz, 9.5 Hz), 3.35–3.40 (m, 1H), 3.47–3.52 (m, 1H), 3.69–3.75 (m, 1H), 3.84–3.89 (m, 2H), 4.03 (t, 2H, J = 6.6 Hz), 4.56–4.58 (m, 1H), 5.01 (t, 1H, J = 2.2 Hz), 6.93 (d, 1H, J = 8.8 Hz), 7.01 (d, 2H, J = 8.8 Hz), 7.07 (d, 1H, J = 6.6 Hz), 7.22 (d, 2H, J = 8.8 Hz), 7.27–7.43 (m, 6H), 7.55 (d, 2H, J = 8.8 Hz), 7.80 (d, 1H, J = 7.3 Hz), 7.91 (d, 1H, J = 1.5 Hz); IR (thin film) 2933, 2857, 1249 cm^{-1}; HRMS (ESI, positive) calcd for $C_{45}H_{54}O_7S_2$ $(M+Na)^+$ 793.3208; obsd 793.3193.

5.54. Phenyl 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-[[5-(tetrahydro-2*H*-pyran-2-yloxy)propyl]oxy]but-2-ynyl]-1,1′-biphenyl-3-sulfonate (31a)

The title compound was synthesized in the same manner as the general procedure for **30**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.4 Hz), 1.45–1.58 (m, 6H), 1.64–1.73 (m, 1H), 1.75–1.92 (m, 5H), 2.22 (d, 1H, J = 5.2 Hz), 3.44-3.52 (m, 2H), 3.60 (t, 2H, J = 6.3 Hz), 3.29–3.87 (m, 2H), 4.03 (t, 2H, J = 6.5 Hz), 4.17 (s, 2H), 4.56 (brs, 1H), 5.06 (d, 1H, J = 5.2 Hz), 6.94 (d, 1H, J = 8.3 Hz), 7.02 (dd, 2H, J = 8.8 Hz, 2.1 Hz), 7.09 (dd, 1H, J = 7.7 Hz, 1.3 Hz), 7.21–7.44 (m, 8H), 7.56 (dd, 2H, J = 8.8 Hz, 2.1 Hz), 7.80 (d, 1H, J = 7.7 Hz), 7.90 (d, 1H, J = 1.9 Hz); IR (thin film) 3390, 2940, 1872, 1592, 1489, 1457, 1387 cm^{-1}; MS (FAB) m/z: 716 $(M)^+$.

5.55. Phenyl 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-[[5-(tetrahydro-2*H*-pyran-2-yloxy)pentyl]oxy]but-2-ynyl]-1,1′-biphenyl-3-sulfonate (31b)

The title compound was synthesized in the same manner as the general procedure for **30**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.4 Hz), 1.38–1.73 (m, 14H), 1.77–1.86 (m, 2H), 2.14 (dd, 1H, J = 1.5 Hz, 5.2 Hz), 3.39 (td, 1H, J = 6.6 Hz, 9.7 Hz), 3.49 (t, 2H, J = 6.5 Hz), 3.45–3.52 (m, 1H), 3.73 (td, 1H, J = 6.8 Hz, 9.7 Hz), 3.82–3.88 (m, 1H), 4.03 (t, 2H, J = 6.5 Hz), 4.16 (d, 2H, J = 1.6 Hz), 4.55–4.58 (m,

1H), 5.07 (td, 1H, J = 1.6 Hz, 5.2 Hz), 6.94 (d, 1H, J = 8.3 Hz), 7.02 (dd, 2H, J = 2.1 Hz, 8.8 Hz), 7.09 (dd, 1H, J = 1.3 Hz, 7.7 Hz), 7.21–7.44 (m, 8H), 7.56 (dd, 2H, J = 2.1 Hz, 8.8 Hz), 7.79 (dd, 1H, J = 1.3 Hz, 7.7 Hz), 7.90 (d, 1H, J = 2.0 Hz); IR (thin film) 3390, 1593, 1489, 1458, 1387, 1368, 1249 cm^{-1}; HRMS (ESI, positive) calcd for $C_{42}H_{48}O_8S_2Na$ $(M+Na)^+$ 767.2688; obsd 767.2690.

5.56. Phenyl 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-[[7-(tetrahydro-2*H*-pyran-2-yloxy)heptyl]oxy]but-2-ynyl]-1,1′-biphenyl-3-sulfonate (31c)

The title compound was synthesized in the same manner as the general procedure for **30**. ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.4 Hz), 1.30–1.39 (m, 6H), 1.48–1.52 (m, 10H), 1.66–1.74 (m, 1H), 1.77–1.86 (m, 3H), 2.04 (dd, 1H, J = 1.5 Hz, 5.2 Hz), 3.39 (td, 1H, J = 6.6 Hz, 9.5 Hz), 3.46 (t, 2H, J = 6.6 Hz), 3.46–3.53 (m, 1H), 3.72 (td, 1H, J = 6.9 Hz, 9.5 Hz), 3.82–3.88 (m, 1H), 4.03 (t, 2H, J = 6.5 Hz), 4.16 (d, 2H, J = 1.7 Hz), 4.55–4.58 (m, 1H), 5.07 (td, 1H, J = 1.7 Hz, 5.2 Hz), 6.94 (d, 1H, J = 8.3 Hz), 7.02 (dd, 2H, J = 2.1 Hz, 8.8 Hz), 7.09 (dd, 1H, J = 1.3 Hz, 7.7 Hz), 7.21–7.44 (m, 8H), 7.56 (dd, 2H, J = 2.1 Hz, 8.8 Hz), 7.79 (dd, 1H, J = 1.3 Hz, 7.7 Hz), 7.90 (d, 1H, J = 2.0 Hz); IR (thin film) 3390, 1593, 1489, 1458, 1388, 1368, 1249 cm^{-1}; HRMS (ESI, positive) calcd for $C_{44}H_{52}O_8S_2Na$ $(M+Na)^+$ 795.3002; obsd 795.3019.

5.57. Phenyl 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-[[9-(tetrahydro-2*H*-pyran-2-yloxy)nonyl]oxy]but-2-ynyl]-1,1′-biphenyl-3-sulfonate (31d)

The title compound was synthesized in the same manner as the general procedure for **30**. ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.4 Hz), 1.24–1.37 (m, 10H), 1.47–1.52 (m, 10H), 1.67–1.75 (m, 1H), 1.77–1.86 (m, 3H), 1.99 (dd, 1H, J = 1.8 Hz, 5.2 Hz), 3.37 (td, 1H, J = 6.7 Hz, 9.6 Hz), 3.46 (t, 2H, J = 6.6 Hz), 3.47–3.53 (m, 1H), 3.72 (td, 1H, J = 6.9 Hz, 9.6 Hz), 3.83–3.90 (m, 1H), 4.03 (t, 2H, J = 6.5 Hz), 4.16 (d, 2H, J = 1.7 Hz), 4.57 (t, 1H, J = 3.6 Hz), 5.07 (dt, 1H, J = 1.7 Hz, 5.2 Hz), 6.94 (d, 1H, J = 8.3 Hz), 7.02 (dd, 2H, J = 2.1 Hz, 8.8 Hz), 7.09 (dd, 1H, J = 1.3 Hz, 7.6 Hz), 7.21–7.44 (m, 8H), 7.56 (dd, 2H, J = 2.1 Hz, 8.8 Hz), 7.79 (dd, 1H, J = 1.2 Hz, 7.8 Hz), 7.90 (d, 1H, J = 2.0 Hz); IR (thin film) 3397, 1593, 1489, 1458, 1388, 1368, 1249 cm^{-1}; HRMS (ESI, positive) calcd for $C_{46}H_{56}O_8S_2Na$ $(M+Na)^+$ 823.3315; obsd 823.3311.

5.58. Phenyl 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-[[11-(tetrahydro-2*H*-pyran-2-yloxy)undecyl]oxy]but-2-ynyl]-1,1′-biphenyl-3-sulfonate (31e)

The title compound was synthesized in the same manner as the general procedure for **30**. ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.4 Hz), 1.23–1.38 (m, 14H), 1.48–1.63 (m, 10H), 1.67–1.75 (m, 1H), 1.78–1.86 (m, 1H), 2.00 (dd, 1H, J = 1.2 Hz, 5.1 Hz), 3.38 (td, 1H, J = 6.7 Hz, 9.6 Hz), 3.46 (t, 2H, J = 6.7 Hz), 3.47–3.53 (m, 1H), 3.72 (td, 1H, J = 6.9 Hz, 9.6 Hz), 3.83–3.90 (m, 1H), 4.03 (t, 2H, J = 6.5 Hz), 4.16 (d, 2H, J = 1.6 Hz), 4.57 (t, 1H, J = 3.5 Hz), 5.06 (td, 1H, J = 1.6 Hz, 5.1 Hz), 6.94 (d, 1H, J = 8.3 Hz), 7.02 (dd, 2H, J = 2.0 Hz, 8.7 Hz), 7.09 (dd, 1H, J = 1.3 Hz, 7.6 Hz), 7.21–7.44 (m, 8H), 7.56 (dd, 2H, J = 2.0 Hz, 8.7 Hz), 7.79 (dd, 1H, J = 1.2 Hz, 7.7 Hz), 7.91 (d, 1H, J = 2.0 Hz); IR (thin film) 3389, 1593, 1489, 1388, 1368, 1249 cm^{-1}; HRMS (ESI, positive) calcd for $C_{48}H_{60}O_8S_2Na$ $(M+Na)^+$ 851.3627; obsd 851.3649.

5.59. Phenyl 4-[(4-butoxyphenyl)thio]-2′-(1,12-dihydroxydodec-2-yn-1-yl)biphenyl-3-sulfonate (32)

p-TsOH (10 mg, 0.01 mmol) was added to a solution of compound **30** (0.10 g, 0.13 mmol) in MeOH (1.0 ml) at room temperature. After stirring for 1 h, Et_3N (1.0 ml) was added to the reaction mixture. The resulting mixture was poured into water and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give the crude product, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (1:1) afforded the title compound (80 mg, 87%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.3 Hz), 1.23–1.38 (brs, 10H), 1.45-1.57 (m, 6H), 1.74–1.84 (m, 2H), 2.20 (dt, 2H, J = 2.0 Hz, 9.5 Hz), 3.61 (t, 2H, J = 6.6 Hz), 4.03 (t, 2H, J = 6.6 Hz), 5.01 (s, 1H), 6.93 (d, 1H, J = 8.1 Hz), 7.01 (d, 2H, J = 8.8 Hz), 7.06 (d, 1H, J = 6.6 Hz), 7.22 (d, 2H, J = 8.1 Hz), 7.27–7.42 (m, 8H), 7.55 (d, 2H, J = 8.8 Hz), 7.80 (d, 1 H, J = 8.8 Hz), 7.91 (d, 1H, J = 2.2 Hz); IR (thin film) 3388, 2931, 1242 cm^{-1}; HRMS (ESI, positive) calcd for $C_{40}H_{46}O_6S_2$ $(M+Na)^+$ 709.2624; obsd 709.2612.

5.60. Phenyl 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-[(3-hydroxypropyl)oxy]but-2-ynyl]-1,1′-biphenyl-3-sulfonate (33a)

The title compound was synthesized in the same manner as the general procedure for **32**. ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H, J = 7.4 Hz), 1.49–1.58 (m, 2H), 1.72–1.83 (m, 4H), 3.55 (t, 2H, J = 6.3 Hz), 3.60 (t, 2H, J = 6.4 Hz), 4.06 (t, 2H, J = 6.4 Hz), 4.14 (d, 2H, J = 1.4 Hz), 4.98 (s, 1H), 6.97 (d, 1H, J = 8.3 Hz), 7.06 (d, 1H, J = 7.6 Hz), 7.09 (d, 2H, J = 8.7 Hz), 7.20 (d, 2H, J = 7.9 Hz), 7.32 (t, 2H, J = 7.6 Hz), 7.37–7.45 (m, 4H), 7.56 (d, 2H, J = 8.7 Hz), 7.76 (d, 1H, J = 7.6 Hz), 7.81 (d, 1H, J = 1.8 Hz); IR (thin film) 3385, 2958, 2934, 2873, 1593, 1489 cm^{-1}; MS (FAB, positive) m/z: 632 $(M)^+$.

5.61. Phenyl 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-[(5-hydroxypentyl)oxy]but-2-ynyl]-1,1′-biphenyl-3-sulfonate (33b)

The title compound was synthesized in the same manner as the general procedure for **32**. ^1H NMR (400 MHz, CD_3OD) δ 1.01 (t, 3H, J = 7.4 Hz), 1.34–1.41 (m, 2H), 1.47–1.58 (m, 6H), 1.77–1.83 (m, 2H), 3.46 (t, 2H, J = 6.5 Hz), 3.51 (t, 2H, J = 6.6 Hz), 4.06 (t, 2H, J = 6.4 Hz), 4.13 (d, 2H, J = 1.6 Hz), 4.99 (brs, 1H),

6.97 (d, 1H, J = 8.3 Hz), 7.06 (d, 1H, J = 7.7 Hz), 7.09 (d, 2H, J = 8.8 Hz), 7.20 (d, 2H, J = 8.1 Hz), 7.30–7.34 (m, 2H), 7.37–7.42 (m, 3H), 7.43 (dd, 1H, J = 1.9 Hz, 8.3 Hz), 7.56 (d, 2H, J = 8.8 Hz), 7.75 (d, 1H, J = 7.7 Hz), 7.82 (d, 1H, J = 1.9 Hz); IR (thin film) 3383, 1593, 1489, 1458, 1387, 1366, 1249 cm^{-1}; HRMS (ESI, positive) calcd for $C_{37}H_{40}O_7S_2Na$ $(M+Na)^+$ 683.2113; obsd 683.2130.

5.62. Phenyl 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-[(7-hydroxyheptyl)oxy]but-2-ynyl]-1,1′-biphenyl-3-sulfonate (33c)

The title compound was synthesized in the same manner as the general procedure for **32**. ^1H NMR (400 MHz, CD_3OD) δ 1.01 (t, 3H, J = 7.4 Hz), 1.28–1.37 (m, 6H), 1.47–1.58 (m, 6H), 1.77–1.83 (m, 2H), 3.44 (t, 2H, J = 6.5 Hz), 3.52 (t, 2H, J = 6.7 Hz), 4.06 (t, 2H, J = 6.4 Hz), 4.12 (d, 2H, J = 1.6 Hz), 4.99 (brs, 1H), 6.97 (d, 1H, J = 8.3 Hz), 7.06 (d, 1H, J = 7.7 Hz), 7.09 (d, 2H, J = 8.7 Hz), 7.20 (d, 2H, J = 8.0 Hz), 7.30–7.35 (m, 2H), 7.37–7.42 (m, 3H), 7.43 (dd, 1H, J = 1.9 Hz, 8.3 Hz), 7.55 (d, 2H, J = 8.7 Hz), 7.75 (d, 1H, J = 7.7 Hz), 7.81 (d, 1H, J = 1.9 Hz); IR (thin film) 3386, 1593, 1489, 1458, 1387, 1366, 1249 cm^{-1}; HRMS (ESI, positive) calcd for $C_{39}H_{44}O_7S_2Na$ $(M+Na)^+$ 711.2426; obsd 711.2427.

5.63. Phenyl 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-[(9-hydroxynonyl)oxy]but-2-ynyl]-1,1′-biphenyl-3-sulfonate (33d)

The title compound was synthesized in the same manner as the general procedure for **32**. ^1H NMR (400 MHz, CD_3OD) δ 1.01 (t, 3H, J = 7.4 Hz), 1.23–1.37 (m, 10H), 1.48–1.58 (m, 6H), 1.77–1.83 (m, 2H), 3.44 (t, 2H, J = 6.5 Hz), 3.53 (t, 2H, J = 6.6 Hz), 4.06 (t, 2H, J = 6.4 Hz), 4.12 (d, 2H, J = 1.6 Hz), 4.99 (brs, 1H), 6.97 (d, 1H, J = 8.3 Hz), 7.06 (d, 1H, J = 7.7 Hz), 7.09 (d, 2H, J = 8.7 Hz), 7.20 (d, 2H, J = 8.2 Hz), 7.32 (t, 2H, J = 7.1 Hz), 7.37–7.41 (m, 3H), 7.43 (dd, 1H, J = 1.9 Hz, 8.3 Hz), 7.56 (d, 2H, J = 8.7 Hz), 7.75 (d, 1H, J = 7.7 Hz), 7.81 (d, 1H, J = 1.9 Hz); IR (thin film) 3383, 1593, 1489, 1458, 1387, 1366, 1249 cm^{-1}; HRMS (ESI, positive) calcd for $C_{41}H_{48}O_7S_2Na$ $(M+Na)^+$ 739.2740; obsd 739.2739.

5.64. Phenyl 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-[(11-hydroxyundecyl)oxy]but-2-ynyl]-1,1′-biphenyl-3-sulfonate (33e)

The title compound was synthesized in the same manner as the general procedure for **32**. ^1H NMR (400 MHz, CD_3OD) δ 1.01 (t, 3H, J = 7.4 Hz), 1.21–1.38 (m, 14H), 1.48–1.58 (m, 6H), 1.77–1.84 (m, 2H), 3.44 (t, 2H, J = 6.5 Hz), 3.53 (t, 2H, J = 6.7 Hz), 4.06 (t, 2H, J = 6.4 Hz), 4.12 (d, 2H, J = 1.5 Hz), 4.99 (brs, 1H), 6.97 (d, 1H, J = 8.3 Hz), 7.06 (d, 1H, J = 7.4 Hz), 7.09 (d, 2H, J = 8.7 Hz), 7.20 (d, 2H, J = 7.8 Hz), 7.32 (t, 2H, J = 7.4 Hz), 7.37–7.42 (m, 3H), 7.43 (dd, 1H, J = 1.9 Hz, 8.3 Hz), 7.56 (d, 2H, J = 8.7 Hz), 7.75 (d, 1H, J = 7.4 Hz), 7.81 (d, 1H, J = 1.9 Hz); IR (thin film) 3376, 1593, 1489, 1458, 1387, 1367, 1249 cm^{-1}; HRMS (FAB, positive) calcd for $C_{43}H_{52}O_7S_2Na$ $(M+Na)^+$ 767.3052; obsd 767.3029.

5.65. Sodium 4-[(4-butoxyphenyl)thio]-2′-(1,12-dihydroxydodec-2-yn-1-yl)biphenyl-3-sulfonate (34)

NaOH (0.10 g, 2.4 mmol) was added to a solution of compound **32** (80 mg, 0.12 mmol) in a mixed solvent of dioxane (1 ml) and water (0.3 ml). After stirring for 8 h at 90 °C, the resulting mixture was purified by silica gel column chromatography. Elution with $MeOH/CH_2Cl_2$ (1:5) afforded the title compound (30 mg, 39%) as an amorphous solid. ^1H NMR (400 MHz, CD_3OD) δ 1.00 (t, 3H, J = 7.3 Hz), 1.27–1.42 (brs, 10H), 1.45 (t, 2H, J = 7.3 Hz), 1.50-1.56 (m, 4H), 1.75–1.91 (m, 2H), 2.17–2.21 (m, 2H), 3.52 (t, 2H, J = 6.6 Hz), 4.03 (t, 2H, J = 6.6 Hz), 5.28 (t, 1H, J = 2.2 Hz), 6.82 (d, 1H, J = 8.1 Hz), 7.01 (d, 2H, J = 8.8 Hz), 7.18-7.24 (m, 2H), 7.32 (dd, 1H, J = 1.5 Hz, 8.8 Hz), 7.38 (dt, 2H, J = 1.5 Hz, 7.3 Hz), 7.55 (dd, 2H, J = 2.2 Hz, 6.6 Hz), 7.78 (dd, 1H, J = 1.5 Hz, 8.1 Hz), 7.98 (d, 1H, J = 2.2 Hz); IR (KBr) 3398, 2929, 1242 cm^{-1}; HRMS (ESI, negative) calcd for $C_{34}H_{41}NaO_6S_2$ $(M-Na)^-$ 609.2345; obsd 609.2351.

5.66. Sodium 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-(3-hydroxypropoxy)but-2-yn-1-yl]biphenyl-3-sulfonate (35a)

The title compound (22 mg, 40% from **33a**) was synthesized in the same manner as the general procedure for compound **34**. ^1H NMR (400 MHz, CD_3OD) δ 1.04 (t, 3H, J = 7.4 Hz), 1.53–1.61 (m, 2H), 1.75–1.86 (m, 4H), 3.60 (t, 2H, J = 6.3 Hz), 3.63 (t, 2H, J = 6.4 Hz), 4.07 (t, 2H, J = 6.4 Hz), 4.20 (d, 2H, J = 1.5 Hz), 5.41 (brs, 1H), 6.87 (d, 1H, J = 8.2 Hz), 7.05 (d, 2H, J = 8.7 Hz), 7.23–7.27 (m, 2H), 7.38 (t, 1H, J = 7.5), 7.44 (t, 1H, J = 7.5 Hz), 7.59 (d, 2H, J = 8.7 Hz), 7.83 (d, 1H, J = 7.5 Hz), 8.03 (d, 1H, J = 1.9 Hz); IR (KBr) 11593, 2873, 2931, 2957, 3399 cm^{-1}; HRMS (ESI, positive) calcd for $C_{29}H_{32}NaO_7S_2$ $(M+H)^+$ 579.1487; obsd 579.1484.

5.67. Sodium 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-[(5-hydroxypentyl)oxy]but-2-yn-1-yl]biphenyl-3-sulfonate (35b)

The title compound (24 mg, 33% from **33b**) was synthesized in the same manner as the general procedure for compound **34**. ^1H NMR (400 MHz, CD_3OD) δ 1.00 (t, 3H, J = 7.4 Hz), 1.33–1.40 (m, 2H), 1.48–1.58 (m, 6H), 1.75–1.83 (m, 2 H), 3.47 (t, 2H, J = 6.5 Hz), 3.52 (t, 2H, J = 6.6 Hz), 4.03 (t, 2H, J = 6.4 Hz), 4.15 (d, 2H, J = 1.6 Hz), 5.37 (brs, 1H), 6.84 (d, 1H, J = 8.2 Hz), 7.01 (d, 2H, J = 8.7 Hz), 7.19–7.23 (m, 2H), 7.34 (dt, 1H, J = 1.2 Hz, 7.5 Hz), 7.40 (dt, 1H, J = 1.2 Hz, 7.5 Hz), 7.55 (d, 2H, J = 8.7 Hz), 7.78 (d, 1H, J = 7.5 Hz), 7.99 (d, 1H, J = 1.9 Hz); IR (KBr) 3399, 1593, 1494, 1458, 1243 cm^{-1}; HRMS (ESI, negative) calcd for $C_{31}H_{35}O_7S_2$ $(M-Na)^-$ 583.1824; obsd 583.1814.

5.68. Sodium 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-[(5-hydroxyheptyl)oxy]but-2-yn-1-yl]biphenyl-3-sulfonate (35c)

The title compound (28 mg, 40% from **33c**) was synthesized in the same manner as the general procedure for compound **34**. ^{1}H NMR (400 MHz, CD_3OD) δ 1.00 (t, 3H, J = 7.4 Hz), 1.31 (brs, 6H), 1.47–1.57 (m, 6H), 1.75–1.82 (m, 2H), 3.46 (t, 2H, J = 6.5 Hz), 3.52 (t, 2H, J = 6.7 Hz), 4.03 (t, 2H, J = 6.4 Hz), 4.15 (d, 2H, J = 1.6 Hz), 5.37 (brs, 1H), 6.83 (d, 1H, J = 8.2 Hz), 7.01 (d, 2H, J = 8.7 Hz), 7.19-7.23 (m, 2H), 7.34 (dt, 1H, J = 1.2 Hz, 7.5 Hz), 7.39 (t, 1H, J = 7.5 Hz), 7.55 (d, 2H, J = 8.7 Hz), 7.79 (d, 1H, J = 7.5 Hz), 7.99 (d, 1H, J = 2.0 Hz); IR (thin film) 3399, 1593, 1493, 1458, 1243 cm^{-1}; HRMS (ESI, negative) calcd for $C_{33}H_{39}O_7S_2$ $(M-Na)^-$ 611.2137; obsd 611.2126.

5.69. Sodium 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-[(5-hydroxynonyl)oxy]but-2-yn-1-yl]biphenyl-3-sulfonate (35d)

The title compound (24 mg, 33% from **33d**) was synthesized in the same manner as the general procedure for compound **34**. ^{1}H NMR (400 MHz, CD_3OD) δ 1.04 (t, 3H, J = 7.4 Hz), 1.32 (brs, 10H), 1.51–1.61 (m, 6H), 1.79–1.86 (m, 2H), 3.49 (t, 2H, J = 6.5 Hz), 3.57 (t, 2H, J = 6.7 Hz), 4.07 (t, 2H, J = 6.4 Hz), 4.19 (d, 2H, J = 1.4 Hz), 4.92 (brs, 1H), 6.87 (d, 1H, J = 8.2 Hz), 7.05 (d, 2H, J = 8.7 Hz), 7.23–7.28 (m, 2H), 7.38 (d, 1H, J = 7.5 Hz), 7.43 (t, 1H, J = 7.5 Hz), 7.59 (d, 2H, J = 8.7 Hz), 7.83 (d, 1H, J = 7.5 Hz), 8.03 (d, 1H, J = 1.8 Hz); IR (thin film) 3376, 1593, 1489, 1458, 1387,1367, 1249 cm^{-1}; HRMS (ESI, negative) calcd for $C_{35}H_{43}O_7S_2$ $(M-Na)^-$ 639.2452; obsd 639.2416.

5.70. Sodium 4-[(4-butoxyphenyl)thio]-2′-[1-hydroxy-4-[(5-hydroxyundecyl)oxy]but-2-yn-1-yl]biphenyl-3-sulfonate (35e)

The title compound (30 mg, 47% from **33e**) was synthesized in the same manner as the general procedure for compound **34**. ^{1}H NMR (400 MHz, CD_3OD) δ 1.04 (t, 3H, J = 7.4 Hz), 1.28-1.42 (m, 14H), 1.52–1.62 (m, 6H), 1.79–1.86 (m, 2H), 3.49 (t, 2H, J = 6.5 Hz), 3.57 (t, 2H, J = 6.7 Hz), 4.07 (t, 2H, J = 6.4 Hz), 4.19 (d, 2H, J = 1.5 Hz), 5.41 (brs, 1H), 6.87 (d, 1H, J = 8.2 Hz), 7.05 (d, 2H, J = 8.7 Hz), 7.23–7.28 (m, 2H), 7.38 (t, 1H, J = 7.5 Hz), 7.43 (t, 1H, J = 7.5 Hz), 7.59 (d, 2H, J = 8.7 Hz), 7.83 (d, 1H, J = 7.5 Hz), 8.03 (d, 1H, J = 1.9 Hz); IR (thin film) 3376, 1593, 1489, 1458, 1387, 1367, 1249 cm^{-1}; HRMS (ESI, negative) calcd for $C_{37}H_{47}O_7S_2$ $(M-Na)^-$ 667.2763; obsd 667.2756.

5.71. cAMP assay

CHO cells stably expressing human $S1P_1$ receptors (CHO–$S1P_1$ cells) were established in our laboratory and maintained in selection medium (α-minimum essential medium without ribonucleosides and deoxyribonucleosides (Invitrogen) containing 10% dialyzed fetal bovine serum (FBS, JRH Biosciences), 100 U/mL penicillin G sodium, and 100 μg/mL streptomycin sulfate (Invitrogen)) with 125 nM methotrexate. CHO–$S1P_1$ cells were seeded into a 96-well plate (4×10^5 cells/well) with the selection medium and cultured overnight. The next day, FBS was removed from the medium, and the cells were preincubated with 1 mM 3-isobutyl-1-methylxanthine (IBMX) for 5 min and then stimulated by 30 μM forskolin with or without 100 nM S1P and various amounts of test compounds for 15 min in the presence of 1 mM IBMX. After the reaction, the cells were dissolved using 1% Triton X-100 and the cyclic adenosine 3′,5′-monophosphate (cAMP) concentration was measured in a competitive assay using a cAMP femtomolar kit (CIS Bio International), following the instructions of the manufacturer (n = 3).

5.72. Selectivity profiling among S1P receptors

For the measurement of human $S1P_1$ and $S1P_4$ receptor signaling, Gqi5 chimeric G proteins were co-expressed with each receptor in CHO cells. Both cell lines and CHO cells stably expressing human $S1P_2$ receptors were established in our laboratory. Fluo3-AM and pluronic acid (Pluronic F-127 low absorbance) were purchased from Molecular Probes. Each receptor-expressing cell was suspended in HAM medium (Invitrogen) containing 10% dialyzed FBS, 100 U/mL penicillin G sodium, and 100 μg/mL streptomycin sulfate (5×10^4 cells/mL for $S1P_1$, $S1P_2$, and $S1P_3$, 1×10^5 cells/mL for $S1P_4$), and seeded into a 384-well plate (Corning 3712) with 50 μL/well and cultured for 2 days. The plate was washed using an ELx405 washer (BIO-TEK INSTRUMENTS) with reaction buffer (Hanks' balanced salt solution without phenol red (Invitrogen), 20 mM Hepes, and 2.5 mM probenecid, pH 7.4) and 25 μL of the buffer being left in each well. Twenty-five microliters of another reaction buffer, containing 4 μM Fluo3-AM and 0.04% (w/v) pluronic acid, was poured into each well and the plate was cultured for 45–60 min, and then washed again in the same way, leaving 15 μL of the buffer. Serial-diluted test compounds were dissolved into the reaction buffer, a 3-fold concentration of the final, and 15 μL of each one was added into the plate. After 10 min of culturing, the plate was set on a FLIPR384 (Molecular Devices) and 15 μL of reaction buffer containing S1P was injected into each well. The intensity of the S1P receptor signaling and inhibitory effects of each of the test compounds were simultaneously measured using the FLIPR384. The final concentrations of S1P were modified for each receptor, at 100 nM, 100 nM, 10 nM, and 10 μM for $S1P_1$–$S1P_4$, respectively.

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8. In the process of our in-house screening, we found that a cAMP assay was a simple and high specific activity measurement method for $S1P_1$ antagonists. Furthermore, since both a [^{32}P] S1P-receptor binding assay and a cAMP assay of a primitive derivative showed almost the same IC_{50} values (data not shown), cAMP assays were mainly used for the evaluation of subsequent derivatives.
9. Although we tried a [^{32}P] S1P-receptor binding assay for the measurement of the acceptor specificity of our compounds, it was unusable because some of our cell strains had an inadequate acceptor expression amount. Therefore, we evaluated the acceptor specificity of the compounds by measuring the inhibition of a compound over the signal transduction of each acceptor subtype.