Development of Novel EDG3 Antagonists Using a 3D Database Search and Their Structure−Activity Relationships

Yuuki Koide,*,†,‡ Takeshi Hasegawa,§ Atsuo Takahashi,† Akira Endo,‖ Naoki Mochizuki,‖ Masako Nakagawa,‡ and Atsushi Nishida*,‡

Drug Research Department, Tokyo Research Laboratories, TOA EIYO Ltd., 2-293-3 Amanuma, Saitama 330-0834, Japan, Graduate School of Pharmaceutical Sciences, Chiba University, 1-33 Yayoicho, Inage, Chiba 263-8522, Japan, Drug Research Department, Fukushima Research Laboratories, TOA EIYO Ltd., 1 Tanaka, Yuno, Iizaka, Fukushima 960-0280, Japan, and Department of Structural Analysis, National Cardiovascular Center Research Institute, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan

Sphingosine-1-phosphate (S1P) is an intracellular second messenger and an extracellular mediator through endothelial differentiation gene (EDG) receptors, which are a novel class of G-protein-coupled receptors. Although EDG has attracted much attention because of its various roles, no selective agonists or antagonists have yet been developed. This could account for the delay in clarifying the physiological roles of members of the EDG family. Because precise structural information on EDG receptors is not yet available, pharmacophore models were generated based on structural information for S1P using the rational drug design software Catalyst. Novel antagonists, 2-alkylthiazolidine-4-carboxylic acids, were retrieved from a three-dimensional database search using the pharmacophore models, and these showed activity for EDG3. On the basis of their nonphosphoric acid structure, more potent antagonists, 2-(*m*- or *p*-heptylphenyl)thiazolidine-4-carboxylic acid, were developed.

Introduction

Sphingosine-1-phosphate (S1P) is a bioactive lipid mediator that has recently been identified as an intracellular second messenger and an extracellular mediator through endothelial differentiation gene (EDG) receptors, which are a novel class of G-protein-coupled receptors (GPCRs).[1−4] Eight subfamilies of EDG have been identified and among them EDG1, 3, 5, 6, and 8 respond principally to S1P. On the other hand, EDG2, 4, and 7 are activated principally by lysophosphatidic acid (LPA).[5−11] Multiple cellular responses to S1P through EDG, including Ca^{2+} mobilization, modulation of adenylyl cyclase, activation of extracellular signal-regulated kinase (ERK), and mitogen-activated protein kinase (MAPK), have been revealed by many pathological and biological studies.[12−14] On the basis of studies of their mitogenic potential through EDG1, 3, and/or 5, S1P antagonists are expected to be effective therapeutic agents for cardiovascular disease and angiogenesis caused by mitogenic cell growth.[15−18]

Suramin is the only reported antagonist of EDG3 and native LPA receptors.[19−21] However, it is not specific for EDG, and various biological activities, such as adenosine 5′-triphosphate (ATP) receptor antagonism,[22,23] cellular DNA primase inhibition,[24] transforming growth factor α (TGF α) inhibition,[25] and fibroblast growth factor (FGF) antagonism,[26] have been reported. Suramin has also been used as a therapeutic agent for filariasis.[27]

Because of its multiple biological activities, suramin is not suitable for studying the pathological functions of EDG.

We searched for a novel and specific EDG1 and/or EDG3 antagonist, which might be suitable as a therapeutic agent for promoting angiogenesis and the proliferation and migration of endothelial cells by the rational drug design approach. A recent study using homology modeling showed three interactions between EDG1 and S1P.[28,29] Considering this structural information, we generated Catalyst pharmacophore models,[30] which are called hypothesis models in Catalyst, for an EDG ligand based on the structure of S1P and searched a three-dimensional (3D) database. Two novel compounds were retrieved from the 3D database,[31] and these showed antagonist activity using Hela cells that overexpressed EDG3.[32] In this paper, we report these novel and effective EDG3 antagonists and their structure−activity relationships.

Results and Discussion

Because S1P has a flexible long alkyl chain, it is difficult to determine its active conformation. Therefore, we generated multiple conformations that should be able to cover the entire conformational space of S1P by Catalyst conformer generation using the Poling method.[33−35] Twenty conformations of S1P within ΔE = 3 kcal mol^{-1} from the minimum energy conformer were chosen.

These conformations were manually transferred into hypothesis models. A homology study suggested interaction between two cationic amino acids, Arg^{120} and Arg^{292}, and the phosphoric acid of S1P with EDG1.[28,29] Furthermore, Glu^{121} was expected to interact with an amino group of S1P. These residues were conserved

* To whom correspondence should be addressed. Y.K.: Tel: +81-(48)6477971. Fax: +81(48)6480078. E-mail: koide.yuuki@toaeiyo.co.jp. A.N.: Tel: +81(43)2902907. Fax: +81(43)2902909. E-mail: nishida@p.chiba-u.ac.jp.
† Tokyo Research Laboratories, TOA EIYO Ltd..
‡ Chiba University.
§ Fukushima Research Laboratories, TOA EIYO Ltd..
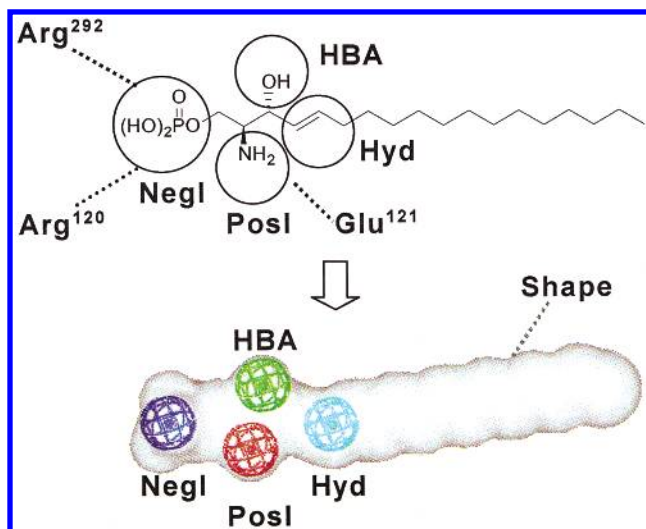‖ National Cardiovascular Center Research Institute.

Figure 1. Generation of Catalyst hypothesis models.

among EDG1, EDG3 (Arg[114], Glu[115], and Lys[279]), and EDG 5 (Arg[108], Glu[109], and Lys[269]). These three interactions could be represented as a positive ionizable feature (PosI) and negative ionizable feature (NegI) in the Catalyst default feature as a blob with 1.5 Å of tolerance (Figure 1). Because 4,5-dihydro-S1P (DHS1P) was less potent than S1P in cells that overexpressed S1P responsive EDGs,[36] the double bond should be important for binding to S1P responsive EDGs. Thus, we made the double bond of S1P a hydrophobic feature (Hyd). The role of the secondary hydroxyl group of S1P

is not yet clear. However, EDG1 and EDG2 can differentiate between S1P and LPA. Therefore, we made the hydroxyl group a hydrogen acceptor feature (HBA). Furthermore, we added a shape feature that describes the molecular volume to within a tolerance of 70–130%. Thus, our hypothesis model consisted of five features: PosI, NegI, Hyd, HBA, and shape. Twenty hypothesis models were generated from 20 conformations (Figure 2). They could be classified into four clusters: straight (S), spherical (SP), bent (B), and extremely bent (EB), according to their shape. Commercially available compounds in the Available Chemical Directory (ACD) database[37] were searched using these hypothesis models as a 3D query. Fifty-eight hit compounds were retrieved from the ACD database. Among the four clusters, the SP cluster gave the most hit compounds. In contrast, no hit compounds were found in the EB cluster.

Thirty-two of the hit compounds (Figure 3), excluding S1P, were evaluated for their ability to inhibit the S1P-induced rapid and transient increase in [Ca^{2+}]$_i$ in Hela cells that overexpressed EDG1 or EDG3 (Hela-EDG1 or Hela-EDG3).[32] We defined compounds that produced inhibition of more than 30% as active. Two compounds, 2-alkylthiazolidine-4-carboxylic acids (**1** and **2**, Maybridge Chemical Co., Ltd., RH00666 and RH00669), showed more than 30% inhibition at 10 μM as EDG3 antagonists and did not increase [Ca^{2+}]$_i$ by themselves. They were also suitable for further optimization as antagonists because of their unique nonphosphoric structure and low molecular weight as compared to
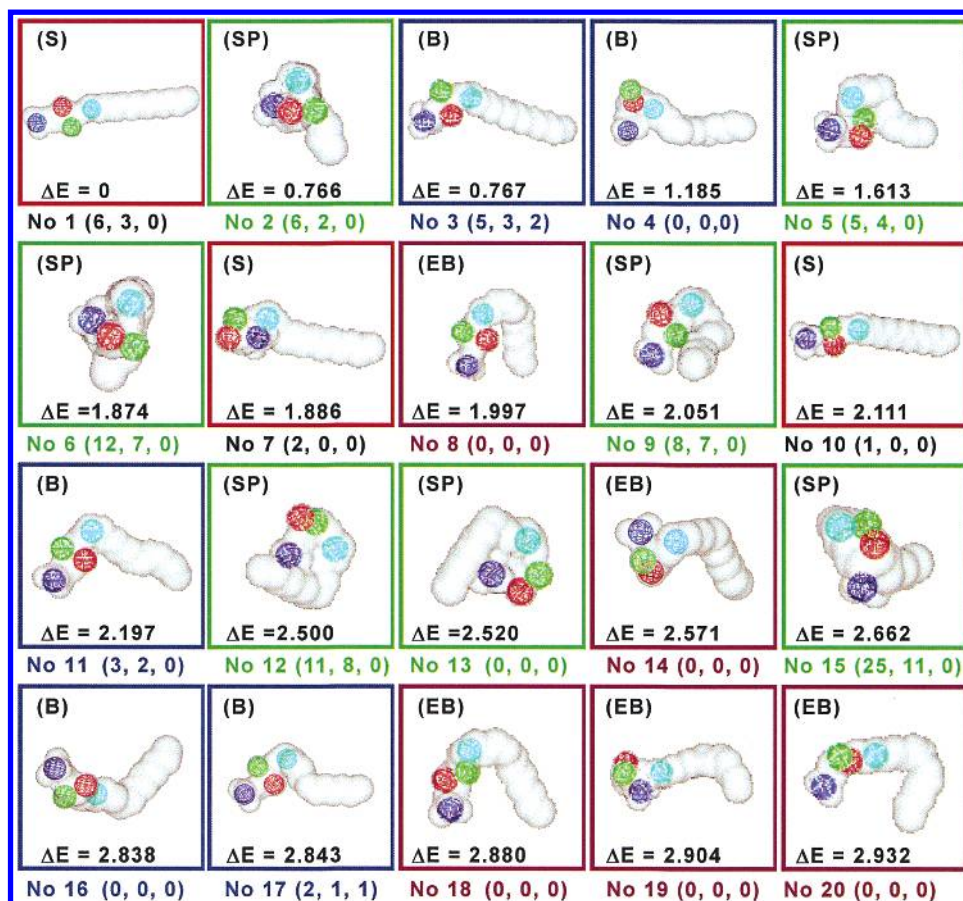

Figure 2. Manually generated Catalyst hypothesis models of S1P. Number of hit compounds, number of tested compounds, and number of active compounds are in parentheses. S, straight conformation; SP, spherical conformation; B, bent conformation; EB, extremely bent conformation. ΔE (kcal mol^{-1}) means the difference in energy from a minimum energy conformer.
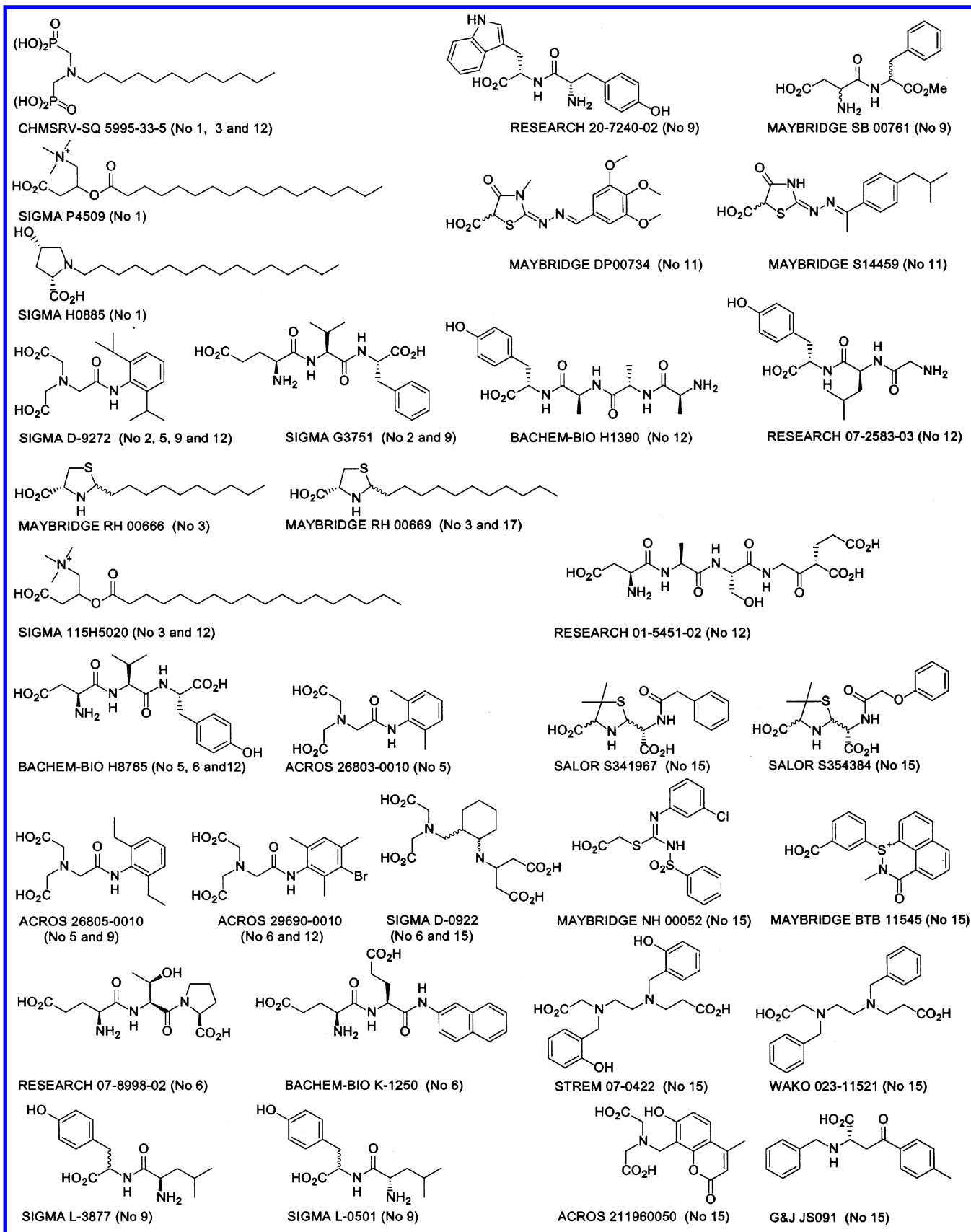
Figure 3. Structures of assayed compounds registered in the ACD99 database. Numbers in parentheses show the hypothesis model that hit the compound.

suramin. According to a ^{1}H NMR study, they were a 1:1 mixture of diastereomers due to a C2 stereogenic center with an (*R*)-configuration at C4.

They were obtained using hypothesis model Nos. 3 and 17, which were classified as cluster B. We assumed that an antagonist would bind the EDG receptor in
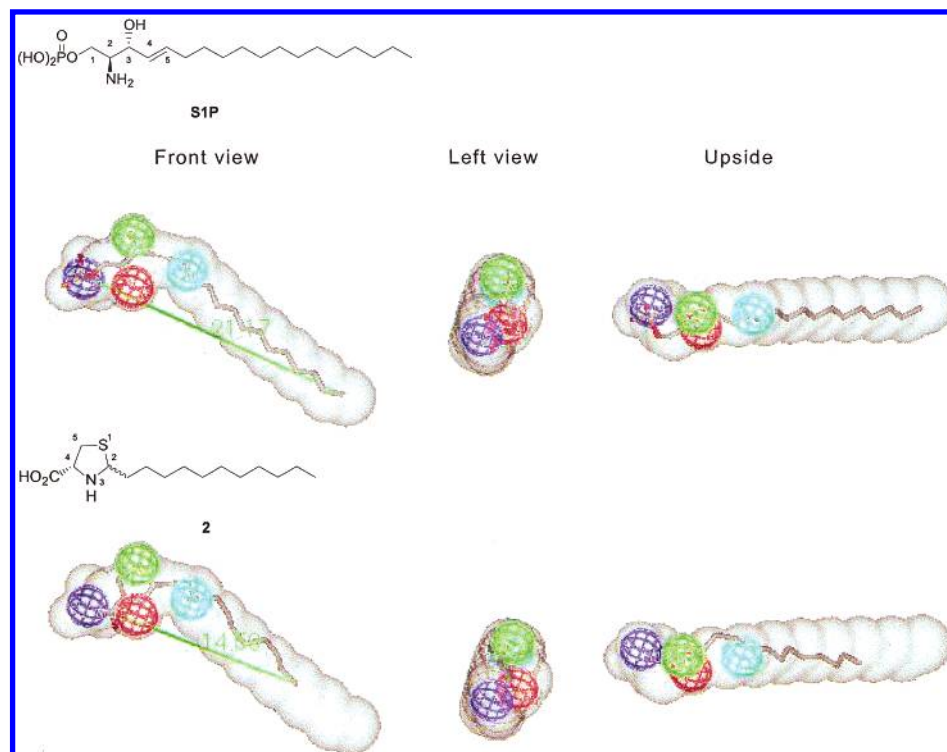
Figure 4. Comparison of two active conformations, S1P and 2-undecyl thiazolidine-4-carboxylic acid **2**, superimposed on hypothesis No. 3.
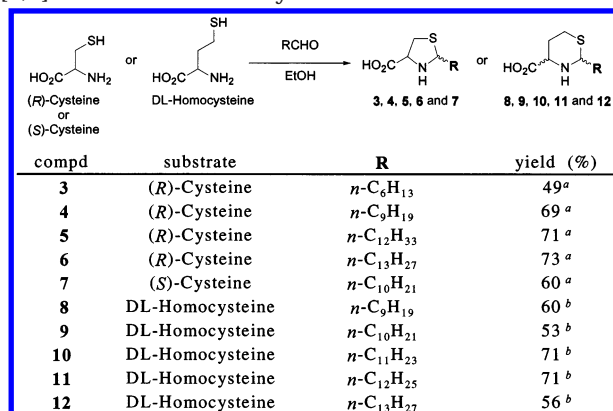
almost the same fashion as the agonist S1P and that the antagonist would lack a critical functional group to cause agonist activity. Although it is not yet known why compounds **1** and **2** show antagonist activity, it may be worth considering several structural features of **2**. The slightly bent conformation of S1P is mainly determined by the dihedral angle of C2−C3−C4−C5, while the related conformation of **2** is governed by the dihedral angle of S1−C2−C6−C7. Compound **2** (14.59 Å) is shorter than S1P (21.17 Å). A difference in electron density at the head part between S1P and **2** might be critical for their difference in activity. Compound **2** was superimposed on hypothesis model No. 3 to compare the active conformations (Figure 4).

Four derivatives, **3**−**6**, were synthesized by known methods to clarify the effect of the molecular length of **2** on its inhibitory activity.[38] We also prepared a stereoisomer **7**, which has an opposite stereocenter at C4, from D-cysteine (Scheme 1). In addition, five racemic thiazinane derivatives, **8**−**12**, were also synthesized.

The lower activity of DHS1P as compared to S1P as a ligand for EDG suggests that the double bond in the chain may play an important role.[36] Although a higher activity was expected with the introduction of a trans double bond at a suitable position in **2**, difficulties in preparing these analogues prompted us to focus on new analogues, **19**−**24**, with an *m*- or *p*-alkylated phenyl ring (Schemes 2 and 3). Recently, it has been reported that the double bond of sphingolipid could be substituted by an *m*- or *p*-alkylated phenyl group.[39] These 18 derivatives were assayed using Hela-EDG1 or Hela-EDG3 cells (Figure 5).

With regard to the alkyl side chain, compound **2**, which has an undecyl group, showed the most potent inhibitory effects in a series of thiazolidine derivatives, **3**−**6**. Five-membered thiazolidine derivatives were su-

Scheme 1. Preparation of 2-Alkylated Thiazolidine and [1,3]Thiazinane-4-carboxylic Acid Derivatives


compd	substrate	R	yield (%)
3	(R)-Cysteine	n-C$_6$H$_{13}$	49[a]
4	(R)-Cysteine	n-C$_9$H$_{19}$	69[a]
5	(R)-Cysteine	n-C$_{12}$H$_{33}$	71[a]
6	(R)-Cysteine	n-C$_{13}$H$_{27}$	73[a]
7	(S)-Cysteine	n-C$_{10}$H$_{21}$	60[a]
8	DL-Homocysteine	n-C$_9$H$_{19}$	60[b]
9	DL-Homocysteine	n-C$_{10}$H$_{21}$	53[b]
10	DL-Homocysteine	n-C$_{11}$H$_{23}$	71[b]
11	DL-Homocysteine	n-C$_{12}$H$_{25}$	71[b]
12	DL-Homocysteine	n-C$_{13}$H$_{27}$	56[b]

[a] Conditions: EtOH, room temperature, 1 h. [b]Conditions: EtOH−H$_2$O, reflux, 12 h.

perior to derivatives of six-membered thiazinane. Compound **7**, which has a (4*S*) configuration and is a stereoisomer of **1**, was less potent than **1**, which has a (4*R*) configuration. 2-(*m* or *p*-Heptylphenyl)thiazolidine-4-carboxylic acids **20** and **23** had the most potent inhibitory effects. Suramin did not have any effect in our assay system. Furthermore, we did not find any compound with obvious inhibitory activity in Hela-EDG1.

Compounds **3** and **4**, which have a side chain of fewer than 10 carbons, were less active than compound **1**. We merged the new hydrophobic feature (Hyd-2) into hypothesis model No. 3 to describe this important hydrophobic interaction (Figure 6A). Compounds **2**, **20**, and **23** were superimposed on this model (Figure 6B). The relative energies of each conformation that fit hypothesis model No. 3′ were 11.7113 kcal mol^{-1} (**2**), 16.0002 kcal mol^{-1} (**20**), and 9.497 76 kcal mol^{-1} (**23**).

Scheme 2. Synthesis of *m*- or *p*-Substituted Benzaldehyde[a]
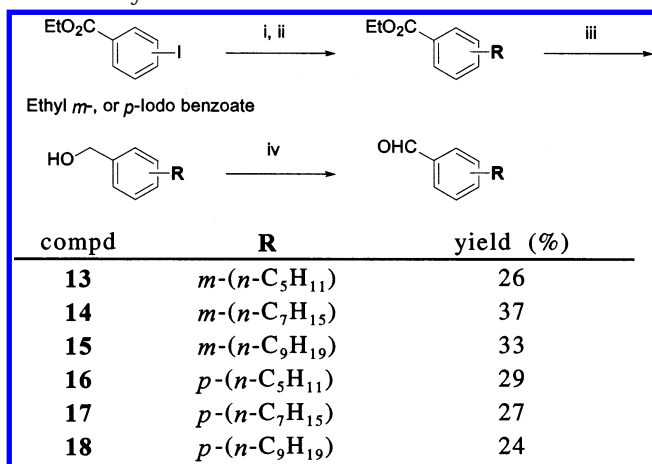
a Reaction conditions: (i) alkyne, PdCl$_2$(PPh$_3$)$_2$, CuI, *i*Pr$_2$NH, CH$_3$CN, room temperature, 12 h. (ii) H$_2$, Pd−C, EtOH, room temperature, 12 h. (iii) LiAlH$_4$, Et$_2$O, room temperature, 1 h. (iv) MnO$_2$, CHCl$_3$, room temperature, 2 h.

Scheme 3. Preparation of 2-(*m*- or *p*-alkylated)phenyl-4-carboxylic Acid Derivatives[a]
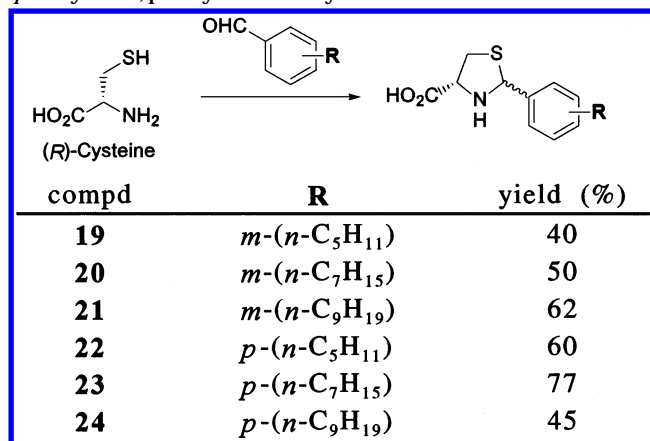
a Conditions: EtOH, room temperature, 12 h.

We estimated the affinity of these derivatives by fit values, which reflect the quality of mapping in a hypothesis model. [40] Fit values were calculated for each optical isomer of all derivatives and adjusted by considering the ratio of diastereomers, since the assay was performed using a mixture of isomers (Table 1). The fit values of thiazolidine derivatives (**1**−**7** and **19**−**24**) were calculated as a 1:1 mixture of diastereomers as determined by ^{1}H NMR study. In thiazinane derivatives (**8**−**12**), nuclear Overhauser effects (NOE) revealed that the major isomers of thiazinane were (2*R*,4*S*) and (2*S*,4*R*). The ratios of diastereomers and enantiomers of thiazinane derivatives were determined to be 7:3 and 1:1, respectively.

The fit values showed good correlations except for compounds with a side chain longer than compound **2**. Further optimization of the hypothesis model is underway.

Conclusion

We generated multiple hypothesis models based on the conformations of S1P. They were used in a 3D query to search a 3D database. Among the 32 compounds assayed, two molecules, 2-alkylthiazolidine-4-carboxylic
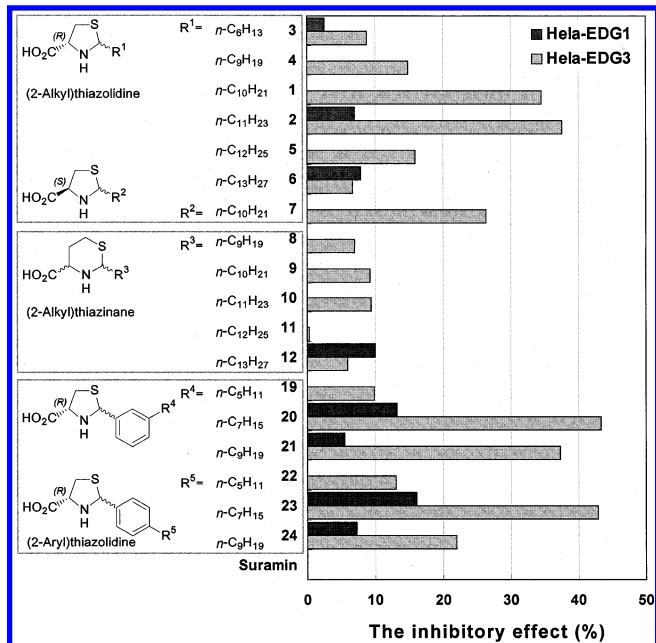

Figure 5. Inhibitory effects of the test compounds (10 μM) on EDG1 and EDG3. The inhibitory effect (%) of the test compound (10 μM) on the S1P (1 μM)-induced increase in [Ca^{2+}]$_i$ in Hela-EDG cells was observed as a difference in RFU from the control.

acids **1** and **2**, showed activity as EDG3 antagonists. These antagonists have a nonphosphoric acid structure with a bent conformation. Further structure optimization led to 2-(*m*-heptylphenyl)thiazolidine-4-carboxylic acid **20**, which may be a new lead compound for the development of therapeutic agents.

Experimental Section

Materials. S1P was purchased from SIGMA and solubilized to 10^{-2} M in dimethyl sulfoxide (DMSO). Dulbecco's modified Eagle's medium (DMEM), Dulbecco's phosphate-buffered saline (+) (D-PBS (+)), and fetal bovine serum (FBS) were also purchased from SIGMA. Minimum essential medium was purchased from GIBCO BRL. The fluorescence reagent Calcium Green-1 AM was purchased from Molecular Probes.

Measurement of [Ca^{2+}]$_i$ Inhibition. Cloned cells expressing EDG1 or 3 (Hela-EDG1 cells or Hela-EDG3 cells) were obtained by transfection of Hela cells with human cDNA of EDG1 or EDG3. Inhibition of the S1P-induced cytoplasmic free calcium concentration ([Ca^{2+}]$_i$) in each cell by each antagonist was measured as described below. Suspensions of Hela-EDG cells in DMEM containing 10% (v/v) FBS were loaded on 96 well plates (approximately 1 × 10^5 cells/well). After they were incubated for 24 h at 37 °C, the cells were washed once with DMEM and then incubated in MEM for 24 h at 37 °C. Cells were washed twice with D-PBS (+) and then maintained with D-PBS (+) containing 5 μM fluorescence reagent Calcium Green-1 AM for 60 min at 37 °C. Cells were washed twice with D-PBS (+). After the cells were maintained with D-PBS (+) for 25 min at 37 °C, they were treated with D-PBS (+) containing 10 μM test compound and incubated for 5 min at 37 °C. After 1 μM S1P was added, fluorescence (excitation at 485 nm; emission at 535 nm) was immediately measured for 30 s at intervals of 3 s with a Fluorescence Ascent FL fluorescence spectrometer (Labsystems). Inhibition was observed as a difference in relative fluorescence units (RFU) between the control, the D-PBS (+) containing 0.1% DMSO, and the test compound. The inhibitory activity was calculated as the average of three wells on the same plate. This experiment was repeated three times on different days, and the inhibitory profiles of the test compounds were identical.

Computational Methods. This study was performed using the software package Catalyst 4.6 (Accelrys Inc., San Diego,
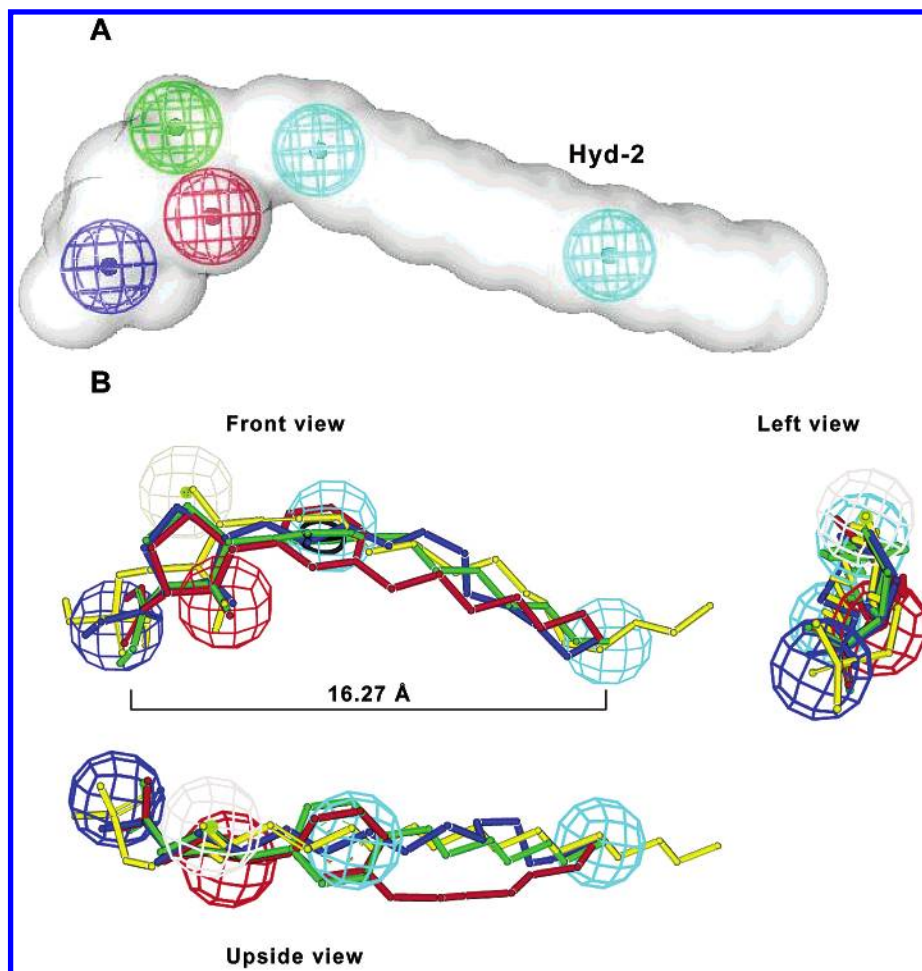
Figure 6. Hypothesis model No. 3′ of S1P and its superimposition. (A) Hypothesis model No. 3′, which incorporated the new hydrophobic feature (Hyd-2). (B) Superimposition of compounds **2**, **20**, and **23**. The shape feature is not shown to clarify the superimposed structures.

Table 1. Fit Values for Each Compound Using Hypothesis Model No. 3′[a]

	compd	4R,2R	4R,2S	4S,2R	4S,2S	avg of fit value	inhibitory effect (%)
3	$R^1 = n\text{-}C_6H_{13}$	0	0			0	0
4	$n\text{-}C_9H_{19}$	2.972 61	0			1.486 31	14.8
1	$n\text{-}C_{10}H_{21}$	3.980 81	3.617 60			3.799 21	34.5
2	$n\text{-}C_{11}H_{23}$	4.148 84	4.146 01			4.147 43	37.6
5	$n\text{-}C_{12}H_{25}$	4.327 97	4.133 71			4.230 84	15.9
6	$n\text{-}C_{13}H_{27}$	4.143 19	4.266 10			4.204 65	6.6
7	$R^2 = n\text{-}C_{10}H_{21}$			3.657 59	3.561 35	3.609 47	26.4
8	$R^3 = n\text{-}C_9H_{19}$	0	0	1.751 16	2.102 86	0.928 34	6.9
9	$n\text{-}C_{10}H_{21}$	0	3.547 35	3.423 95	3.896 10	3.024 37	9.3
10	$n\text{-}C_{11}H_{23}$	3.693 91	3.894 07	3.130 57	4.422 34	3.676 06	9.4
11	$n\text{-}C_{12}H_{25}$	2.720 14	4.114 95	3.524 18	3.137 55	3.552 35	0.3
12	$n\text{-}C_{13}H_{27}$	3.723 02	3.991 27	3.878 61	4.610 82	4.004 53	5.9
19	$R^4 = n\text{-}C_5H_{11}$	0	0			0	9.9
20	$n\text{-}C_7H_{15}$	3.890 05	3.420 23			3.655 14	43.4
21	$n\text{-}C_9H_{19}$	4.110 05	3.334 08			3.722 07	37.2
22	$R^5 = n\text{-}C_5H_{11}$	2.673 94	0			1.336 97	13.0
23	$n\text{-}C_7H_{15}$	4.378 12	3.843 41			4.110 77	42.9
24	$n\text{-}C_9H_{19}$	4.250 51	4.331 90			4.291 21	21.9

[a] Absolute ring configurations are described. Data on the inhibitory effect are the same as those in Figure 5.

CA). All calculations were conducted on an SGI Octane (R 8000), running under the IRIX 6.5.4 operating system. Conformational models for S1P were calculated using a 16 kcal mol^{−1} energy cutoff for the "best quality" conformational search option. Conformational models for other compounds were calculated using a 20 kcal mol^{−1} energy cutoff for the best quality. The number of conformers generated for each molecule was limited to a maximum of 255 and ensured maximum coverage in the conformational space. A hypothesis model consisted of HBA, Hyd, positive ionizable (PosI), negative

ionizable (NegI), and shape features, as shown in Figure 2. The shape feature had a tolerance of within 70−130% of molecular volume similarity, and other blob features had a tolerance of 1.5 Å. To compare and fit a compound with a hypothesis model, the best fit mode was selected.

Chemistry. General Information. Melting points were determined with a Yanako MP-500V micromelting point apparatus (uncorrected), and ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL-300, using $CDCl_3$, CD_3OD, or DMSO-d_6 as solvents, with Me_4Si as an internal standard.

Mass spectra were recorded on either a JEOL HX-110A (FAB) or Finnigan LCQ (ESI). Elemental analyses were performed by Toray Research Center, Inc. Reactions were monitored by TLC analysis using E. Merck silica gel 60F$_{254}$ thin layer plates. Flash chromatography was carried out on E. Merck Kieselgel 60 (230−400 mesh) silica gel. Thirteen thiazolidine derivatives, **1**−**7** and **19**−**24**, were reported as diastereomeric mixtures [(2*R*,4*R*) and (2*S*,4*R*)]. Five thiazinane derivatives, **8**−**12**, were racemic and were reported as diastereomeric mixtures [(2*R**,4*R**) and (2*S**,4*R**)].

m-Pentylbenzaldehyde (13). To a solution of ethyl 3-iodobenzoate (5.29 g, 19.16 mmol) in CH$_3$CN (50 mL) were added 1-pentyne (1.9 mL, 14.12 mmol), diisopropylamine (2.5 mL, 17.66 mmol), dichlorobis(triphenylphosphine)palladium (83 mg, 0.12 mmol), and copper iodide (45 mg, 0.24 mmol) at 0 °C. The mixture was stirred for 12 h, diluted with Et$_2$O, washed sequentially with 5% KHSO$_4$, 5% Na$_2$S$_2$O$_3$, and brine, dried over Na$_2$SO$_4$, filtered, and concentrated. Column chromatography (100:1 hexane:Et$_2$O) provided *m*-(1-pentynyl)-benzoic acid ethyl ester as an orange oil.

The oil was dissolved in EtOH (25 mL), and 10% Pd/C was added (0.53 g). A balloon of hydrogen gas was attached, and the reaction was stirred rapidly for 12 h, filtered through a pad of Celite, and concentrated. Short column chromatography (100:1 hexane:AcOEt) provided *m*-pentylbenzoic acid ethyl ester as a yellow oil.

After the ester was dissolved in Et$_2$O (100 mL), the solution was added dropwise into a suspension of lithium aluminum hydride (471 mg, 12.40 mmol) in Et$_2$O (50 mL) over more than 15 min. The reaction was stirred for 2 h at 0 °C, diluted with Et$_2$O (50 mL), and quenched with MeOH (5 mL). Saturated Rochelle salt (50 mL) was then added to the mixture and stirred for 1 h. The product was extracted with Et$_2$O, and the ether solution was washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated. Column chromatography (100:1 hexane:AcOEt) provided *m*-pentylbenzyl alcohol as a pale yellow oil.

The alcohol was dissolved in CH$_2$Cl$_2$ (50 mL), and activated manganese oxide was added (WAKO Pure Chemical Industries, Ltd.) (5.90 g, 67.85 mmol). The mixture was stirred for 2 h, manganese oxide was filtered off through a pad of Celite, and the filtrate was concentrated. Column chromatography (100:1 hexane:Et$_2$O) provided compound **13** as a colorless oil (886 mg, 5.03 mmol, 26% from ethyl 3-iodobenzoate). ^{1}H NMR (300 MHz, CDCl$_3$): δ 10.00 (s, 1H, CHO), 7.70−7.68 (m, 2H, 2, 5-ArH), 7.45−7.43 (m, 2H, 4, 6-ArH), 2.68 (t, *J* = 7.52 Hz, 2H, 1′-CH$_2$), 1.70−1.62 (m, 2H, 2′-CH$_2$), 1.40−1.31 (m, 4H, CH$_2$), 0.90 (t, *J* = 6.97 Hz, 3H, 5′-CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 192.67 (CHO), 143.96 (C3), 136.49 (C1), 134.72 (C4), 129.32 (C2), 128.87 (C5), 127.51 (C6), 35.59 (C1′), 31.37 (C2′), 30.94 (C3′), 22.47 (C4′), 13.98 (C5′). MS (FAB): *m*/*z* 177 (MH$^+$). HRMS (FAB) calcd for C$_{12}$H$_{17}$O (MH$^+$), 177.2628; found, 177.1264.

m-Heptylbenzaldehyde (14). Compound **14** was prepared according to the procedure described for **13** but using 1-heptyne instead of 1-pentyne. Compound **14** was obtained as a colorless oil (953 mg, 4.67 mmol, 37% from ethyl 3-iodobenzoate). ^{1}H NMR (300 MHz, CDCl$_3$): δ 10.01 (s, 1H, CHO), 7.71−7.70 (m, 2H, 2, 5-ArH), 7.45−7.43 (m, 2H, 4, 6-ArH), 2.68 (t, *J* = 7.34 Hz, 2H, 1′-CH$_2$), 1.67−1.59 (m, 2H, 2′-CH$_2$), 1.42−1.28 (m, 8H, CH$_2$), 0.88 (t, *J* = 6.24 Hz, 3H, 7′-CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 192.68 (CHO), 143.99 (C3), 136.50 (C1), 134.72 (C4), 129.33 (C2), 128.88 (C5), 127.50 (C6), 35.63 (C1′), 31.75 (C2′), 31.27, 29.17, 29.11, 22.64 (C6′), 14.81 (C7′). MS (FAB) *m*/*z* 205 (MH$^+$). HRMS (FAB) calcd for C$_{14}$H$_{21}$O (MH$^+$), 205.3159; found, 205.1591.

m-Nonylbenzaldehyde (15). Compound **15** was prepared according to the procedure described for **13** but using 1-nonyne instead of 1-pentyne. Compound **15** was obtained as a colorless oil (1.31 g, 5.63 mmol, 33% from ethyl 3-iodobenzoate). ^{1}H NMR (300 MHz, CDCl$_3$): δ 10.00 (s, 1H, CHO), 7.84−7.83 (m, 2H, 2, 5-ArH), 7.69−7.68 (m, 2H, 4, 6-ArH), 2.68 (t, *J* = 7.42 Hz, 2H, 1′-CH$_2$), 1.68−1.58 (m, 2H, 2′-CH$_2$), 1.30−1.24 (m, 12H, CH$_2$), 0.88 (t, *J* = 6.79 Hz, 3H, 9′-CH$_3$). ^{13}C NMR (75 MHz,

CDCl$_3$): δ 192.63 (CHO), 143.96 (C3), 136.49 (C1), 134.69 (C4), 129.31 (C2), 128.86 (C5), 127.47 (C6), 35.61 (C1′), 31.84 (C2′), 31.24, 29.48, 29.42, 29.27, 29.19, 22.64 (C8′), 14.08 (C9′). MS (FAB) *m*/*z* 232 (M$^+$). HRMS (FAB) calcd for C$_{16}$H$_{24}$O (M$^+$), 232.3612; found, 232.1774.

p-Pentylbenzaldehyde (16). Compound **16** was prepared according to the procedure described for **13** but using ethyl 4-iodobenzoate instead of ethyl 3-iodobenzoate. Compound **16** was obtained as a colorless oil (605 mg, 3.44 mmol, 29% from ethyl 4-iodobenzoate). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.97 (s, 1H, CHO), 7.79 (d, *J* = 8.08 Hz, 2H, 2, 6-ArH), 7.33 (d, *J* = 8.08 Hz, 2H, 3, 5-ArH), 2.68 (t, *J* = 7.89 Hz, 2H, 1′-CH$_2$), 1.66−1.59 (m, 2H, 2′-CH$_2$), 1.32−1.21 (m, 8H, CH$_2$), 0.88 (t, *J* = 6.79 Hz, 3H, 7′-CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 192.06 (CHO), 150.52 (C4), 134.36 (C1), 129.89 (C2, 6), 129.07 (C3, 5), 36.16 (C1′), 31.41 (C2′), 30.75 (C3′), 22.47 (C4′), 13.96 (C5′). MS (FAB) *m*/*z* 176 (M$^+$). HRMS (FAB) calcd for C$_{12}$H$_{16}$O (M$^+$), 176.1201; found, 176.1193.

p-Heptylbenzaldehyde (17). Compound **17** was prepared according to the procedure described for **16** but using 1-heptyne instead of 1-pentyne. Compound **17** was obtained as a colorless oil (636 mg, 3.12 mmol, 27% from ethyl 4-iodobenzoate). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.97 (s, 1H, CHO), 7.79 (d, *J* = 7.89 Hz, 2H, 2, 6-ArH), 7.33 (d, *J* = 7.89 Hz, 2H, 3, 5-ArH), 2.71−2.66 (t, *J* = 7.52 Hz, 2H, 1′-CH$_2$), 1.67−1.60 (m, 2H, 2′-CH$_2$), 1.35−1.30 (m, 4H, CH$_2$), 0.90 (t, *J* = 6.79 Hz, 3H, 7′-CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 192.04 (CHO), 150.49 (C4), 134.36 (C1), 129.88 (C2, 6), 129.06 (C3, 5), 36.21 (C1′), 31.75 (C2′), 31.08, 29.21, 29.10, 22.62 (C6′), 13.96 (C7′). MS (FAB) *m*/*z* 205 (MH$^+$). HRMS (FAB) calcd for C$_{14}$H$_{21}$O (MH$^+$), 205.1592; found, 205.1585.

p-Nonylbenzaldehyde (18). Compound **18** was prepared according to the procedure described for **16** but using 1-nonyne instead of 1-pentyne. Compound **18** was obtained as a colorless oil (573 mg, 2.47 mmol, 24% from ethyl 4-iodobenzoate). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.97 (s, 1H, CHO), 7.79 (d, *J* = 7.89 Hz, 2H, 2, 6-ArH), 7.33 (d, *J* = 7.89 Hz, 2H, 3, 5-ArH), 2.68 (t, *J* = 7.52 Hz, 2H, 1′-CH$_2$), 1.64−1.56 (m, 2H, 2′-CH$_2$), 1.30−1.26 (m, 12H, CH$_2$), 0.88 (t, *J* = 6.79 Hz, 3H, 9′-CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 191.99 (CHO), 150.46 (C4), 134.33 (C1), 129.84 (C2, 6), 129.02 (C3, 5), 36.17 (C1′), 31.82 (C2′), 31.04, 29.45, 29.40, 29.25, 29.20, 22.62 (C8′), 14.06 (C9′). MS (FAB) *m*/*z* 233 (MH$^+$). HRMS (FAB) calcd for C$_{16}$H$_{25}$O (MH$^+$), 233.1905; found, 233.1912.

(2*R*,4*R*)- and (2*S*,4*R*)-2-Decylthiazolidine-4-carboxylic Acid (1). Compound **1** was synthesized from L-cysteine hydrochloride monohydrate and 1-undecanal according to a procedure described previously.[37] Compound **1** was obtained as a colorless powder (1.01 g, 3.69 mmol, 69%); mp 154−155 °C (lit.[38] 153−154 °C). ^{1}H NMR (300 MHz, CD$_3$OD): δ 4.73 (dd, *J* = 8.89, 5.14 Hz, app 0.5H, 2-CH), 4.59 (dd, *J* = 8.07, 5.51 Hz, app 0.5H, 2-CH), 4.29 (t, *J* = 6.97 Hz, app 0.5H, 4-CH), 4.08 (t, *J* = 7.71 Hz, app 0.5H, 4-CH), 3.41−3.32 (m, app 1.5H, 5-CH$_2$), 3.15 (dd, *J* = 11.01, 8.26 Hz, app 0.5H, 5-CH$_2$), 2.06−2.01 (m, 1H, 1′-CH$_2$), 1.82−1.70 (m, 1H, 1′-CH$_2$), 1.45−1.29 (m, 16H, CH$_2$), 0.89 (t, *J* = 6.61 Hz, 3H, 10′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 172.87 (C=O), 172.32 (C=O), 71.07 (C4), 70.34 (C4), 65.21 (C2), 64.13 (C2), 36.98 (C1′), 36.71 (C1′), 34.82, 31.28, 28.96 (C5), 28.94 (C5), 28.88 (C2′), 28.83 (C2′), 28.77, 28.69, 27.57, 27.37, 22.09 (C9′), 13.94 (C10′). MS (ESI) *m*/*z* 274 (MH$^+$). Anal. (C$_{14}$H$_{27}$NO$_2$S) calcd: C, 61.50; H, 9.95; N, 5.12. Found: C, 61.33; H, 9.77; N, 5.09.

(2*R*,4*R*)- and (2*S*,4*R*)-2-Undecylthiazolidine-4-carboxylic Acid (2). Compound **2** was prepared according to the procedure described for **1** but using 1-dodecanal instead of 1-undecanal. Compound **2** was obtained as a colorless powder (941 mg, 3.27 mmol, 53%); mp 153−154 °C (lit.[38] 151−152 °C). ^{1}H NMR (300 MHz, CD$_3$OD): δ 4.75 (dd, *J* = 9.18, 5.14 Hz, app 0.5H, 2-CH), 4.59 (dd, *J* = 8.08, 5.51 Hz, app 0.5H, 2-CH), 4.30 (t, *J* = 6.98 Hz, app 0.5H, 4-CH), 4.09 (t, *J* = 7.34 Hz, app 0.5H, 4-CH), 3.42−3.27 (m, app 1.5H, 5-CH$_2$), 3.16 (dd, *J* = 11.19, 8.07 Hz, app 0.5H, 5-CH$_2$), 2.04−2.00 (m, 1H, 1′-CH$_2$), 1.84−1.76 (m, 1H, 1′-CH$_2$), 1.43−1.29 (m, 14H, CH$_2$), 0.89 (t, *J* = 6.97 Hz, 3H, 9′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ

172.89 (C=O), 172.31 (C=O), 71.09 (C4), 70.38 (C4), 65.21 (C2), 64.13 (C2), 36.98 (C1′), 36.69 (C1′), 34.82, 31.29, 28.92 (C5), 28.89 (C5), 28.83 (C2′), 28.79 (C2′), 28.65, 27.57, 27.34, 22.09 (C10′), 13.95 (C11′). MS (ESI) m/z 288 (MH$^+$). Anal. (C$_{15}$H$_{29}$NO$_2$S) calcd: C, 62.67; H, 10.17; N, 4.87. Found: C, 62.57; H, 9.95; N, 5.05.

(2R,4R)- and (2S,4R)-2-Hexylthiazolidine-4-carboxylic Acid (3). Compound **3** was prepared according to the procedure described for **1** but using 1-heptanal instead of 1-undecanal. Compound **3** was obtained as a colorless powder (650 mg, 2.99 mmol, 49%); mp 149−150 °C. ^{1}H NMR (300 MHz, CD$_3$OD): δ 4.73 (dd, J = 9.18, 5.32 Hz, app 0.5H, 2-CH), 4.58 (dd, J = 8.08, 5.51 Hz, app 0.5H, 2-CH), 4.30 (t, J = 6.80 Hz, app 0.5H, 4-CH), 4.07 (t, J = 7.34 Hz, app 0.5H, 4-CH), 3.42−3.32 (m, app 1.5H, 5-CH$_2$), 3.15 (dd, J = 11.01, 8.17 Hz, app 0.5H, 5-CH$_2$), 2.04−1.99 (m, 1H, 1′-CH$_2$), 1.84−1.76 (m, 1H, 1′-CH$_2$), 1.38−1.33 (m, 8H, CH$_2$), 0.91 (t, J = 6.79 Hz, 3H, 7′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.86 (C=O), 172.33 (C=O), 71.08 (C4), 70.34 (C4), 65.27 (C2), 64.15 (C2), 36.99 (C1′), 36.65 (C1′), 34.83 (C4), 31.16 (C3′), 28.47 (C5), 28.41 (C5), 27.52 (C2′), 27.32 (C2′), 21.98 (C5′), 13.90 (C6′). MS (ESI) m/z 218 (MH$^+$). Anal. (C$_{10}$H$_{19}$NO$_2$S) calcd: C, 55.26; H, 8.81; N, 6.44. Found: C, 55.15; H, 8.66; N, 6.59.

(2R,4R)- and (2S,4R)-2-Nonylthiazolidine-4-carboxylic Acid (4). Compound **4** was prepared according to the procedure described for **1** but using 1-decanal instead of 1-undecanal. Compound **4** was obtained as a colorless powder (1.09 g, 4.20 mmol, 69%); mp 153−154 °C (lit.[38] 156−157 °C). ^{1}H NMR (300 MHz, CD$_3$OD): δ 4.73 (dd, J = 8.99, 5.14 Hz, app 0.5H, 2-CH), 4.52 (dd, J = 8.26, 5.51 Hz, app 0.5H, 2-CH), 4.28 (t, J = 6.80 Hz, app 0.5H, 4-CH), 4.06 (t, J = 7.34 Hz, app 0.5H, 4-CH), 3.42−3.35 (m, app 1.5H, 5-CH$_2$), 3.13 (dd, J = 11.01, 7.07 Hz, app 0.5H, 5-CH$_2$), 2.06−1.99 (m, 1H, 1′-CH$_2$), 1.83−1.76 (m, 1H, 1′-CH$_2$), 1.35−1.29 (m, 14H, CH$_2$), 0.90 (t, J = 6.97 Hz, 3H, 9′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.85 (C=O), 172.33 (C=O), 71.05 (C4), 70.29 (C4), 65.29 (C2), 64.14 (C2), 37.01 (C1′), 36.75 (C1′), 34.82, 31.26, 28.93 (C5), 28.88 (C5), 28.82 (C2′), 28.75 (C2′), 28.65, 27.55, 27.34, 22.07 (C8′), 13.91 (C9′). MS (ESI) m/z 260 (MH$^+$). Anal. (C$_{13}$H$_{25}$NO$_2$S) calcd: C, 60.19; H, 9.71; N, 5.40. Found: C, 60.09; H, 9.54; N, 5.59.

(2R,4R)- and (2S,4R)-2-Dodecylthiazolidine-4-carboxylic Acid (5). Compound **5** was prepared according to the procedure described for **1** but using 1-tridecanal instead of 1-undecanal. Compound **5** was obtained as a colorless powder (1.32 g, 4.38 mmol, 71%); mp 151−152 °C. ^{1}H NMR (300 MHz, CD$_3$OD): δ 4.74 (dd, J = 8.99, 5.08 Hz, app 0.5H, 2-CH), 4.60 (dd, J = 8.26, 5.01 Hz, app 0.5H, 2-CH), 4.30 (t, J = 6.79 Hz, app 0.5H, 4-CH), 4.10 (t, J = 7.52 Hz, app 0.5H, 4-CH), 3.42−3.37 (m, app 1.5H, 5-CH$_2$), 3.17 (dd, J = 11.19, 8.08 Hz, app 0.5H, 5-CH$_2$), 2.07−2.00 (m, 1H, 1′-CH$_2$), 1.84−1.76 (m, 1H, 1′-CH$_2$), 1.32−1.30 (m, 20H, CH$_2$), 0.90 (t, J = 6.79 Hz, 3H, 12′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.85 (C=O), 172.28 (C=O), 71.07 (C4), 70.33 (C4), 65.16 (C2), 64.11 (C2), 36.95 (C1′), 36.68 (C1′), 34.81, 31.27, 28.98 (C5), 28.92 (C5), 28.86 (C2′), 28.80 (C2′), 28.75, 28.68, 27.55, 28.68, 27.55, 27.35, 22.07 (C11′), 13.91 (C12′). MS (ESI) m/z 302 (MH$^+$). Anal. (C$_{16}$H$_{31}$NO$_2$S) calcd: C, 63.74; H, 10.36; N, 4.65. Found: C, 63.68; H, 10.18; N, 4.83.

(2R,4R)- and (2S,4R)-2-Tridecylthiazolidine-4-carboxylic Acid (6). Compound **6** was prepared according to the procedure described for **1** but using 1-tetradecanal instead of 1-undecanal. Compound **6** was obtained as a colorless powder (1.41 g, 4.47 mmol, 73%); mp 151−152 °C (lit.[38] 148−149 °C). ^{1}H NMR (300 MHz, CD$_3$OD): δ 4.73 (dd, J = 8.99, 5.14 Hz, app 0.5H, 2-CH), 4.58 (dd, J = 8.26, 5.51 Hz, app 0.5H, 2-CH), 4.29 (t, J = 7.17 Hz, app 0.5H, 4-CH), 4.07 (t, J = 7.52 Hz, app 0.5H, 4-CH), 3.42−3.35 (m, app 1.5H, 5-CH$_2$), 3.14 (dd, J = 11.01, 8.07 Hz, app 0.5H, 5-CH$_2$), 2.04−2.01 (m, 1H, 1′-CH$_2$), 1.83−1.76 (m, 1H, 1′-CH$_2$), 1.35−1.29 (m, 22H, CH$_2$), 0.90 (t, J = 6.97 Hz, 3H, 13′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.87 (C=O), 172.32 (C=O), 71.10 (C4), 70.36 (C4), 65.23 (C2), 64.14 (C2), 36.98 (C1′), 36.68 (C1′), 34.82, 31.27, 28.99, 28.69, 27.55, 27.36, 22.07 (C12′), 13.93 (C13′). MS (ESI) m/z 316

(MH$^+$). Anal. (C$_{17}$H$_{33}$NO$_2$S) calcd: C, 64.71; H, 10.54; N, 4.44. Found: C, 64.69; H, 10.31; N, 4.64.

(2R,4R)- and (2S,4R)-2-Decylthiazolidine-4-carboxylic Acid (7). Compound **7** was prepared according to the procedure described for **1** but using D-cysteine instead of L-cysteine. Compound **7** was obtained as a colorless powder (1.01 g, 3.69 mmol, 60%); mp 153−154 °C. ^{1}H NMR (300 MHz, CD$_3$OD): δ 4.74 (dd, J = 8.81, 5.14 Hz, app 0.5H, 2-CH), 4.60 (dd, J = 8.26, 5.69 Hz, app 0.5H, 2-CH), 4.30 (t, J = 7.16 Hz, app 0.5H, 4-CH), 4.09 (t, J = 7.52 Hz, app 0.5H, 4-CH), 3.42−3.37 (m, app 1.5H, 5-CH$_2$), 3.16 (dd, J = 11.10, 8.26 Hz, app 0.5H, 5-CH$_2$), 2.06−2.00 (m, 1H, 1′-CH$_2$), 1.84−1.76 (m, 1H, 1′-CH$_2$), 1.31−1.27 (m, 16H, CH$_2$), 0.90 (t, J = 6.79 Hz, 3H, 10′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.84 (C=O), 172.28 (C=O), 71.06 (C4), 70.32 (C4), 65.16 (C2), 64.11 (C2), 36.95 (C1′), 36.68 (C1′), 34.81, 31.27, 28.96 (C5), 28.93 (C5), 28.87 (C2′), 28.81 (C2′), 28.76, 27.68, 27.55, 27.35, 22.07 (C9′), 13.91 (C10′). MS (ESI) m/z 274 (MH$^+$). Anal. (C$_{14}$H$_{27}$NO$_2$S) calcd: C, 61.50; H, 9.95; N, 5.12. Found: C, 61.42; H, 9.84; N, 5.30.

(2R,4R)- and (2S,4R)-2-(m-Pentylphenyl)thiazolidine-4-carboxylic Acid (19). Compound **19** was prepared according to the procedure described for **1** but using m-pentylbenzaldehyde **13** instead of 1-undecanal. Compound **19** was obtained as a colorless powder (206 mg, 0.74 mmol, 40%); mp 153−154 °C. ^{1}H NMR (300 MHz, CD$_3$OD): δ 7.38−7.28 (m, 4H, ArH), 5.73 (s, app 0.5H, 2-CH), 5.55 (s, app 0.5H, 2-CH), 4.40 (dd, J = 7.81, 4.34 Hz, app 0.5H, 4-CH), 4.08 (t, J = 7.52 Hz, app 0.5H, 4-CH), 3.51 (dd, J = 10.46, 7.52 Hz, app 1H, 5-CH$_2$), 3.39 (dd, J = 15.78, 4.93 Hz, app 1H, 5-CH$_2$), 2.63 (t, J = 7.34 Hz, 2H, 1′-CH$_2$), 1.66−1.63 (m, 2H, 2′-CH$_2$), 1.36−1.34 (m, 4H, CH$_2$), 0.88 (t, J = 7.16 Hz, 3H, 5′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.02 (C=O), 172.22 (C=O), 142.66 (ArC3), 142.36 (ArC3), 140.91 (ArC1), 138.77 (ArC1), 128.36 (ArC2), 128.25 (ArC5), 128.12 (ArC2) 127.57 (ArC5), 127.11 (ArC4), 126.83 (ArC4), 124.63 (ArC6), 124.33 (ArC6), 71.87 (C4), 71.24 (C4), 65.43 (C2), 64.88 (C2), 38.41 (C5′), 37.94 (C5′), 35.09 (C1′), 35.03 (C1′), 30.92 (C2′), 30.66 (C2′), 21.94 (C4′), 13.92 (C5′). MS (ESI) m/z 280 (MH$^+$). Anal. (C$_{15}$H$_{21}$NO$_2$S) calcd: C, 64.48; H, 7.58; N, 5.01. Found: C, 64.33; H, 7.58; N, 5.19.

(2R,4R)- and (2S,4R)-2-(m-Heptylphenyl)thiazolidine-4-carboxylic Acid (20). Compound **20** was prepared according to the procedure described for **1** but using m-heptylbenzaldehyde **14** instead of 1-undecanal. Compound **20** was obtained as a colorless powder (49 mg, 0.16 mmol, 50%); mp 142−144 °C. ^{1}H NMR (300 MHz, CD$_3$OD): δ 7.37−7.28 (m, 4H, ArH), 5.73 (s, app 0.5H, 2-CH), 5.55 (s, app 0.5H, 2-CH), 4.40 (dd, J = 7.16, 4.77 Hz, app 0.5H, 4-CH), 4.08 (t, J = 7.16 Hz, app 0.5H, 4-CH), 3.51 (dd, J = 10.64, 7.16 Hz, app 1H, 5-CH$_2$), 3.40 (dd, J = 11.01, 4.77 Hz, app 1H, 5-CH$_2$), 2.63 (t, J = 8.08 Hz, 2H, 1′-CH$_2$), 1.64−1.62 (m, 2H, 2′-CH$_2$), 1.33−1.30 (m, 8H, CH$_2$), 0.89 (t, J = 6.42 Hz, 3H, 7′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.27 (C=O), 172.45 (C=O), 142.92 (ArC3), 142.62 (ArC3), 141.17 (ArC1), 139.03 (ArC1), 128.62 (ArC2), 128.50 (ArC5), 128.38 (ArC2) 127.84 (ArC5), 127.37 (ArC4), 127.09 (ArC4), 124.89 (ArC6), 124.58 (ArC6), 72.13 (C4), 71.49 (C4), 65.68 (C2), 65.13 (C2), 38.67 (C5), 38.21 (C5), 35.38 (C1′), 35.32 (C1′), 31.51 (C2′), 31.25 (C2′), 28.91, 28.77, 22.33 (C6′), 14.21 (C7′). MS (ESI) m/z 308 (MH$^+$). Anal. (C$_{17}$H$_{25}$NO$_2$S) calcd: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.33; H, 8.10; N, 4.74.

(2R,4R)- and (2S,4R)-2-(m-Nonylphenyl)thiazolidine-4-carboxylic Acid (21). Compound **21** was prepared according to the procedure described for **1** but using m-nonylbenzaldehyde **15** instead of 1-undecanal. Compound **21** was obtained as a colorless powder (356 mg, 1.06 mmol, 62%); mp 130−131 °C. ^{1}H NMR (300 MHz, CD$_3$OD): δ 7.37−7.16 (m, 4H, ArH), 5.73 (s, app 0.5H, 2-CH), 5.56 (s, app 0.5H, 2-CH), 4.42 (dd, J = 7.16, 4.77 Hz, app 0.5H, 4-CH), 4.10 (t, J = 7.52 Hz, app 0.5H, 4-CH), 3.50 (dd, J = 10.54, 7.52 Hz, app 1H, 5-CH$_2$), 3.40 (dd, J = 10.83, 4.77 Hz, app 1H, 5-CH$_2$), 2.63 (t, J = 7.89 Hz, 2H, 1′-CH$_2$), 1.63−1.60 (m, 2H, 2′-CH$_2$), 1.33−1.29 (m, 12H, CH$_2$), 0.89 (t, J = 6.97 Hz, 3H, 9′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.01 (C=O), 172.21 (C=O), 142.65

(ArC3), 142.35 (ArC3), 140.92 (ArC1), 138.75 (ArC1), 128.34 (ArC2), 128.24 (ArC5), 128.11 (ArC2) 127.56 (ArC5), 127.11 (ArC4), 126.84 (ArC4), 124.62 (ArC6), 124.31 (ArC6), 71.87 (C4), 71.24 (C4), 65.43 (C2), 64.88 (C2), 38.42 (C5), 37.95 (C5), 35.12 (C1′), 35.07 (C1′), 32.42, 31.27 (C2′), 30.98 (C2′), 28.98, 28.97, 28.86, 28.69, 22.09 (C8′), 13.95 (C9′). MS (ESI) m/z 336 (MH$^+$). Anal. (C$_{19}$H$_{29}$NO$_2$S) calcd: C, 68.02; H, 8.71; N, 4.17. Found: C, 67.80; H, 8.51; N, 4.40.

(2R,4R)- and (2S,4R)-2-(p-Pentylphenyl)thiazolidine-4-carboxylic Acid (22). Compound **22** was prepared according to the procedure described for **1** but using p-pentylbenzaldehyde **16** instead of 1-undecanal. Compound **22** was obtained as a colorless powder (182 mg, 0.65 mmol, 60%); mp 159−160 °C. ^{1}H NMR (300 MHz, CD$_3$OD): 7.46 (dd, J = 8.07, 3.30 Hz, 2H, ArH) 7.21 (dd, J = 3.30, 8.07 Hz, 2H, ArH), 5.73 (s, app 0.5H, 2-CH), 5.55 (s, app 0.5H, 2-CH), 4.40 (dd, J = 12.84, 4.96 Hz, app 0.5H, 4-CH), 4.07 (t, J = 7.34 Hz, app 0.5H, 4-CH), 3.54−3.48 (m, app 1H, 5-CH$_2$), 3.40 (dd, J = 11.02, 4.96 Hz, app 1H, 5-CH$_2$), 2.62 (t, J = 8.81 Hz, 2H, 1′-CH$_2$), 1.64−1.62 (m, 2H, 2′-CH$_2$), 1.34−1.31 (m, 4H, CH$_2$), 0.89 (t, J = 7.16 Hz, 3H, 5′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.02 (C= O), 172.24 (C=O), 142.54 (ArC4), 142.80 (ArC4), 138.24 (ArC1), 136.09 (ArC1), 128.36 (ArC2, 6), 128.11 (ArC2, 6), 127.18 (ArC3, 5) 126.91 (ArC3, 5), 71.71 (C4), 71.10 (C4), 65.36 (C2), 64.84 (C2), 38.45 (C5), 37.93 (C5), 34.77 (C1′), 34.74 (C1′), 30.86 (C3′), 30.62 (C2′), 30.59 (C2′), 21.94 (C4′), 13.91 (C5′). MS (ESI) m/z 280 (MH$^+$). Anal. (C$_{15}$H$_{21}$NO$_2$S) calcd: C, 64.48; H, 7.58; N, 5.01. Found: C, 64.27; H, 7.59; N, 5.21.

(2R,4R)- and (2S,4R)-2-(p-Heptylphenyl)thiazolidine-4-carboxylic Acid (23). Compound **23** was prepared according to the procedure described for **1** but using p-heptylbenzaldehyde **17** instead of 1-undecanal. Compound **23** was obtained as a colorless powder (158 mg, 0.51 mmol, 77%); mp 154−156 °C. ^{1}H NMR (300 MHz, CD$_3$OD): 7.47 (dd, J = 8.07, 3.30 Hz, 2H, ArH) 7.21 (dd, J = 3.30, 8.07 Hz, 2H, ArH), 5.73 (s, app 0.5H, 2-CH), 5.56 (s, app 0.5H, 2-CH), 4.40 (dd, J = 7.34, 4.77 Hz, app 0.5H, 4-CH), 4.09 (t, J = 7.34 Hz, app 0.5H, 4-CH), 3.55−3.50 (m, app 1H, 5-CH$_2$), 3.45 (dd, J = 16.88, 4.77 Hz, app 1H, 5-CH$_2$), 2.61 (t, J = 7.16 Hz, 2H, 1′-CH$_2$), 1.63−1.61 (m, 2H, 2′-CH$_2$), 1.32−1.29 (m, 8H, CH$_2$), 0.89 (t, J = 6.97 Hz, 3H, 7′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.92 (C= O), 172.15 (C=O), 142.45 (ArC4), 141.69 (ArC4), 138.15 (ArC1), 136.00 (ArC1), 128.26 (ArC2, 6), 128.01 (ArC2, 6), 127.08 (ArC3, 5) 126.81 (ArC3, 5), 71.62 (C4), 71.00 (C4), 65.27 (C2), 64.75 (C2), 38.36 (C5), 37.83 (C5), 34.71 (C1′), 34.68 (C1′), 31.15, 30.86 (C2′), 30.83 (C2′), 28.52, 28.42, 21.98 (C6′), 13.85 (C7′). MS (ESI) m/z 308 (MH$^+$). Anal. (C$_{17}$H$_{25}$NO$_2$S) calcd: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.25; H, 8.16; N, 4.76.

(2R,4R)- and (2S,4R)-2-(p-Nonylphenyl)thiazolidine-4-carboxylic Acid (24). Compound **24** was prepared according to the procedure described for **1** but using p-nonylbenzaldehyde **18** instead of 1-undecanal. Compound **24** was obtained as a colorless powder (135 mg, 0.40 mmol, 45%); mp 130−131 °C. ^{1}H NMR (300 MHz, CD$_3$OD): 7.46 (dd, J = 8.02, 3.30 Hz, 2H, ArH), 7.20 (dd, J = 3.30, 8.02 Hz, 2H, ArH), 5.74 (s, app 0.5H, 2-CH), 5.57 (s, app 0.5H, 2-CH), 4.41 (dd, J = 7.34, 4.95 Hz, app 0.5H, 4-CH), 4.10 (t, J = 7.34 Hz, app 0.5H, 4-CH), 3.55−3.50 (m, app 1H, 5-CH$_2$), 3.45 (dd, J = 16.88, 4.95 Hz, app 1H, 5-CH$_2$), 2.62 (t, J = 6.61 Hz, 2H, 1′-CH$_2$), 1.63−1.61 (m, 2H, 2′-CH$_2$), 1.32−1.89 (m, 12H, CH$_2$), 0.89 (t, J = 6.42 Hz, 3H, 9′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.00 (C=O), 172.23 (C=O), 142.53 (ArC4), 141.77 (ArC4), 138.25 (ArC1), 136.08 (ArC1), 128.34 (ArC2, 6), 128.08 (ArC2, 6), 127.15 (ArC3, 5) 126.88 (ArC3, 5), 71.71 (C4), 71.07 (C4), 65.37 (C2), 64.83 (C2), 38.46 (C5), 37.91 (C5), 34.79 (C1′), 34.75 (C1′), 31.24, 30.92 (C2′), 30.89 (C2′), 28.93, 28.84, 28.66, 28.62, 22.06 (C8′), 13.93 (C9′). MS (ESI) m/z 336 (MH$^+$). Anal. (C$_{19}$H$_{29}$NO$_2$S) calcd: C, 68.02; H, 8.71; N, 4.17. Found: C, 67.87; H, 8.48; N, 4.39.

(2R*,4R*)- and (2S*,4R*)-2-Nonyl-1,3-thiazinane-4-carboxylic Acid (8). 1-Decanal (500 mg, 3.69 mmol) was added to a stirred DL-homocysteine (500 mg, 3.69 mmol) in aqueous ethanol (75%, 100 mL). The reaction was refluxed for 12 h. After it was cooled to room temperature, the precipitate was filtered and washed with water and diethyl ether to give a colorless powder. Recrystallization from boiling isopropyl alcohol gave compound **8** as a colorless powder (611 mg, 2.23 mmol, 60%); mp 140−141 °C. ^{1}H NMR (300 MHz, CD$_3$OD): 4.67 (dd, J = 8.81, 4.96 Hz, app 0.3H, 2-CH), 4.30 (dd, J = 10.09, 4.04 Hz, app 0.7H, 2-CH), 3.90 (t, J = 4.59 Hz, app 0.3H, 4-CH), 3.51 (dd, J = 12.66, 2.75 Hz, app 0.7H, 4-CH), 3.04 (app t, app 0.6H, 6-CH$_2$), 2.86−2.80 (m, app 1.4H, 6-CH$_2$), 2.75−2.63 (m, 2H, 5-CH$_2$), 1.97−1.74 (m, 2H, 1′-CH$_2$), 1.35−1.28 (m, 14H, CH$_2$), 0.89 (t, J = 6.97 Hz, 3H, 9′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.36 (C=O), 61.22 (C4), 58.96 (C2), 38.67 (C6), 35.88 (C5), 31.28 (C1′), 28.91, 28.72, 28.68, 28.52, 27.49, 25.30, 22.09 (C8′), 13.94 (C9′). MS (ESI) m/z 274 (MH$^+$). Anal. (C$_{14}$H$_{27}$NO$_2$S) calcd: C, 61.50; H, 9.95; N, 5.12. Found: C, 61.47; H, 9.97; N, 5.29.

(2R*,4R*)- and (2S*,4R*)-2-Decyl-1,3-thiazinane-4-carboxylic Acid (9). Compound **9** was prepared according to the procedure described for **8** but using 1-undecanal instead of 1-decanal. Compound **9** was obtained as a colorless powder (560 mg, 1.95 mmol, 53%); mp 148−149 °C. ^{1}H NMR (300 MHz, CD$_3$OD): 4.66 (dd, J = 13.76, 4.96 Hz, app 0.3H, 2-CH), 4.31 (dd, J = 9.91, 3.85 Hz, app 0.7H, 2-CH), 3.90 (t, J = 4.58 Hz, app 0.3H, 4-CH), 3.49 (dd, J = 12.66, 2.75 Hz, app 0.7H, 4-CH), 3.04 (app t, app 0.6H, 6-CH$_2$), 2.86−2.81 (m, app 1.4H, 6-CH$_2$), 2.73−2.58 (m, 2H, 5-CH$_2$), 1.93−1.74 (m, 2H, 1′-CH$_2$), 1.33−1.30 (m, 16H, CH$_2$), 0.90 (t, J = 6.79 Hz, 3H, 10′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.34 (C=O), 61.20 (C4), 58.96 (C2), 38.67 (C6), 35.87 (C5), 31.30 (C1′), 28.98, 28.90, 28.71, 28.52, 27.49, 25.31, 22.10 (C9′), 13.95 (C10′). MS (ESI) m/z 288 (MH$^+$). Anal. (C$_{15}$H$_{29}$NO$_2$S) calcd: C, 62.67; H, 10.17; N, 4.87. Found: C, 62.65; H, 9.97; N, 5.05.

(2R*,4R*)- and (2S*,4R*)-2-Undecyl-1,3-thiazinane-4-carboxylic acid (10). Compound **10** was prepared according to the procedure described for **8** but using 1-dodecanal instead of 1-decanal. Compound **10** was obtained as a colorless powder (792 mg, 2.63 mmol, 71%); mp 150−151 °C. ^{1}H NMR (300 MHz, CD$_3$OD): 4.68 (dd, J = 8.63, 4.95 Hz, app 0.3H, 2-CH), 4.31 (dd, J = 9.91, 4.04 Hz, app 0.7H, 2-CH), 3.90 (t, J = 4.77 Hz, app 0.3H, 4-CH), 3.49 (dd, J = 12.66, 2.75 Hz, app 0.7H, 4-CH), 3.04 (app t, app 0.6H, 6-CH$_2$), 2.86−2.81 (m, app 1.4H, 6-CH$_2$), 2.72−2.60 (m, 2H, 5-CH$_2$), 1.93−1.77 (m, 2H, 1′-CH$_2$), 1.33−1.29 (m, 18H, CH$_2$), 0.90 (t, J = 6.97 Hz, 3H, 11′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.34 (C=O), 61.20 (C4), 58.96 (C2), 38.67 (C6), 35.87 (C5), 31.30 (C1′), 29.01, 28.97, 28.91, 28.72, 28.52, 27.49, 25.31, 22.10 (C10′), 13.94 (C11′). MS (ESI) m/z 302 (MH$^+$). Anal. (C$_{16}$H$_{31}$NO$_2$S) calcd: C, 63.74; H, 10.36; N, 4.65. Found: C, 63.78; H, 10.15; N, 4.83.

(2R*,4R*)- and (2S*,4R*)-2-Dodecyl-1,3-thiazinane-4-carboxylic Acid (11). Compound **11** was prepared according to the procedure described for **8** but using 1-tridecanal instead of 1-decanal. Compound **11** was obtained as a colorless powder (831 mg, 2.63 mmol, 71%); mp 146−147 °C. ^{1}H NMR (300 MHz, CD$_3$OD): 4.67 (dd, J = 8.49, 5.51 Hz, app 0.3H, 2-CH), 4.31 (dd, J = 9.91, 4.04 Hz, app 0.7H, 2-CH), 3.90 (t, J = 4.77 Hz, app 0.3H, 4-CH), 3.50 (dd, J = 12.66, 2.75 Hz, app 0.7H, 4-CH), 3.04 (app t, app 0.6H, 6-CH$_2$), 2.86−2.81 (m, app 1.4H, 6-CH$_2$), 2.75−2.60 (m, 2H, 5-CH$_2$), 1.94−1.73 (m, 2H, 1′-CH$_2$), 1.35−1.29 (m, 16H, CH$_2$), 0.90 (t, J = 7.16 Hz, 3H, 10′-CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.37 (C=O), 61.23 (C4), 58.92 (C2), 38.67 (C6), 35.91 (C5), 31.27 (C1′), 28.99, 28.93, 28.88, 28.69, 28.50, 27.48, 25.29, 22.08 (C11′), 13.93 (C12′). MS (ESI) m/z 316 (MH$^+$). Anal. (C$_{17}$H$_{33}$NO$_2$S) calcd: C, 64.71; H, 10.54; N, 4.44. Found: C, 64.64; H, 10.36; N, 4.63.

(2R*,4R*)- and (2S*,4R*)-2-Tridecyl-1,3-thiazinane-4-carboxylic Acid (12). Compound **12** was prepared according to the procedure described for **8** but using 1-tetradecanal instead of 1-decanal. Compound **12** was obtained as a colorless powder (408 mg, 1.24 mmol, 56%); mp 136−137 °C. ^{1}H NMR (300 MHz, CD$_3$OD): 4.70−4.66 (m, app 0.3H, 2-CH), 4.32 (dd, J = 9.91, 4.04 Hz, app 0.7H, 2-CH), 3.90 (app t, app 0.3H, 4-CH), 3.47 (dd, J = 12.66, 2.94 Hz, app 0.7H, 4-CH), 3.04 (app t, app 0.6H, 6-CH$_2$), 2.86−2.81 (m, app 1.4H, 6-CH$_2$), 2.63−2.59 (m, 2H, 5-CH$_2$), 1.92−1.77 (m, 2H, 1′-CH$_2$), 1.35−1.26 (m, 22H, CH$_2$), 0.90 (t, J = 6.98 Hz, 3H, 13′-CH$_3$). ^{13}C

NMR (75 MHz, DMSO-d_6): δ 173.38 (C=O), 61.23 (C4), 58.93 (C2), 38.67 (C6), 35.91 (C5), 31.28 (C1′), 29.00, 28.94, 28.70, 28.51, 27.49, 25.30, 22.09 (C12′), 13.93 (C13′). MS (ESI) *m/z* 330 (MH$^+$). Anal. ($C_{18}H_{35}NO_2S$) calcd: C, 65.60; H, 10.71; N, 4.25. Found: C, 65.52; H, 10.50; N, 4.45.

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