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SYNTHESIS AND EVALUATION OF THE ANTITUMOR ACTIVITIES OF TWO SERIES OF JASPINE B ANALOGUES BEARING 2-ALKYLOXYMETHYL GROUP

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Abstract – Two series of jaspine B analogues bearing 2-alkyloxymethyl group have been synthesized and evaluated for their cytotoxicity against four cancer cell lines, including Eca-109, EC-9706, B16-F10 and MCF-7 cells. Most of the compounds exhibited potent cytotoxic activity against all four cell lines. The results also revealed that some of the analogues prepared in the current study exhibited comparable or better in vitro antitumor activity to jaspine B. Compound **9g**, in particular, displayed the most potent antitumor activity of all of the compounds prepared in the current study with an IC_{50} value of 2.0 ± 0.4 μM towards B16-F10 cells, which was better than that of jaspine B (IC_{50} = 5.08 ± 0.6 μM). The results of a structure–activity relationship study showed that the oxygen atom and the length of the alkyl chain have an effect on the cytotoxic activity of these compounds.

INTRODUCTION

Jaspine B (**1**, Figure 1), which is also known as pachastrissamine, was first isolated from the Okinawa marine sponge *Pachastrissa* sp. by Higa[1] and reported to exhibit pronounced cytotoxic activity against P388, A549, HT29 and MEL-28 cells (IC_{50} = 0.01 μg/mL). Shortly after, Debitus[2] reported the extraction of the same naturally occurring anhydrophytosphingosine derivative from another marine sponge *Jaspis* sp. and named it jaspine B. Jaspine B has been reported to inhibit the activity of sphingomyelin synthase,

and regulate the formation of ceramide to induce apoptosis.[3] Jaspine B and its seven stereoisomers have been reported to inhibit sphingosine kinases (SphKs) and atypical protein kinase C as well as the activated caspase pathway following the induction of apoptosis.[4] Most notably, jaspine B has been shown to exhibit excellent antitumor activity.[1,2,5-8]

Based on its pronounced biological activity, jaspine B and its analogues have attracted considerable interest from researchers working in numerous fields, including synthetic and medicinal chemistry. Several jaspine B analogues have consequently been synthesized bearing modified aliphatic chains or amino groups (e.g., **2–4**) and evaluated in terms of their biological activity.[3,9-12] However, most of the analogues synthesized to date exhibited lower or similar levels of cytotoxicity to jaspine B towards several cancer cell lines, including B16 and A375 melanoma cells.

Jaspine B exhibits greater cytotoxic activity towards A549 cells than its stereoisomers, as well as several different configurations of its corresponding phytosphingosines.[5] These results therefore indicate that the stereochemical configuration of the chiral tetrahydrofuran ring of jaspine B plays a significant role in determining its biological activity. Five different stereoisomers of the aza-analogue of jaspine B (**5a**) were prepared and evaluated in terms of their cytotoxic activity.[13] The results revealed that these analogues exhibited almost the same activity as jaspine B against three tumor cell lines. The sulfur, selenium and carbon analogues of jaspine B (**5b–d**) were also reported in the literature, where the tetrahydrofuran core of jaspine B was bioisosterically replaced with tetrahydrothiophene, tetrahydroselenophene and cyclopentane, respectively.[7,14] The sulfur analogue **5b** generally exhibited greater cytotoxicity than jaspine B towards a wide range of cancer cell lines, whereas the selenium (**5c**) and carbon (**5d**) analogues of jaspine B exhibited slightly lower or comparable levels of cytotoxicity to the natural product.

Considerable research efforts have directed towards the development of new methods for the synthesis of jaspine B because of its interesting structural characteristics.[8,10,15-28] The most commonly used methods for the synthesis of jaspine B include the use of a Wittig[27] or Ru-mediated cross-metathesis[20] to allow for the introduction of the long alkyl chain at the 2-position of the tetrahydrofuran ring. The development of new methods for the simple and efficient introduction of the long alkyl chains required of jaspine B derivatives is therefore highly desired. From the perspective of developing a diversity-oriented strategy for the synthesis of jaspine B analogues, a new method allowing for the efficient introduction of alkyl chains bearing a wide range of functional groups would be advantageous for the synthesis of new jaspine

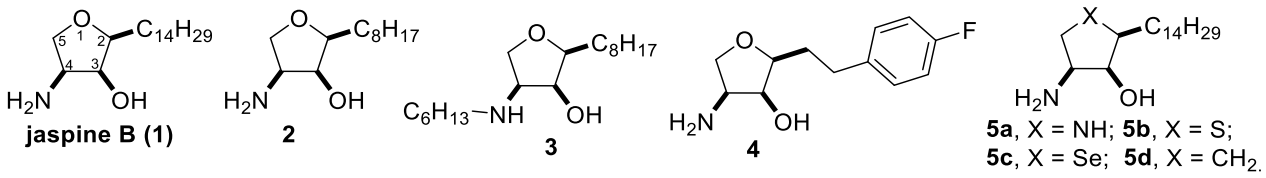
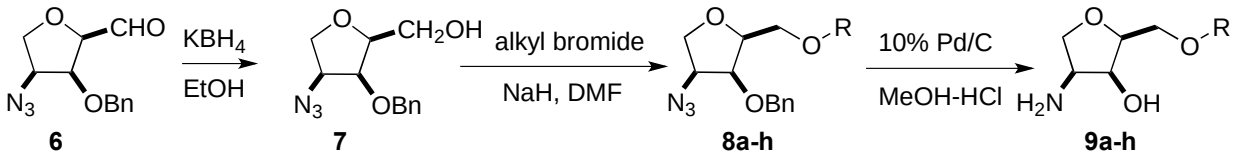


Figure 1. Jaspine B and some of its representative derivatives

B derivatives. During our recent investigations towards the synthesis of jaspine B[16] and its analogues,[29] we developed two new series of jaspine B analogues bearing 2-alkyloxymethyl group. Herein, we describe the synthesis and biological evaluation of the compounds belonging to these two series.

RESULTS AND DISCUSSION

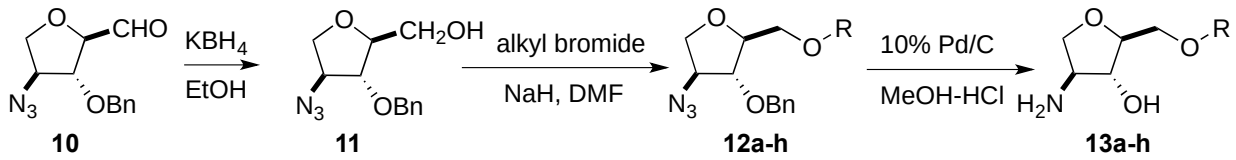
The route used for the synthesis of the jaspine B analogues bearing 2-alkyloxymethyl group **9a–h** is outlined in **Scheme 1**. The reduction of aldehyde **6**[29] using KBH_4 gave the corresponding alcohol **7**, which was reacted with alkyl bromide in the presence of sodium hydride to yield compound **8**. The palladium-catalyzed hydrogenolysis of **8** led to the reduction of the azide functionality to the corresponding amine, with the concomitant removal of the benzyl protecting group to give the target compound **9**.



8a, 9a: R = $(CH_2)_6Me$ **8e**, **9e**: R = $(CH_2)_{11}Me$
8b, **9b**: R = $(CH_2)_7Me$ **8f**, **9f**: R = $(CH_2)_{13}Me$
8c, **9c**: R = $(CH_2)_8Me$ **8g**, **9g**: R = $(CH_2)_{15}Me$
8d, **9d**: R = $(CH_2)_9Me$ **8h**, **9h**: R = $(CH_2)_{17}Me$

Scheme 1. Synthesis of the jaspine B analogues bearing 2-alkyloxymethyl group **9a–h**

The route used for the synthesis of the 3-*epi*-jaspine B analogues bearing 2-alkyloxymethyl group **13a–h** is outlined in **Scheme 2**. All of these compounds were synthesized from aldehyde **10**[29] according to the procedure described in **Scheme 1**. The structures of all of the newly synthesized compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy, as well as high resolution mass spectrometry.



12a, **13a**: R = $(CH_2)_6Me$ **12e**, **13e**: R = $(CH_2)_{11}Me$
12b, **13b**: R = $(CH_2)_7Me$ **12f**, **13f**: R = $(CH_2)_{13}Me$
12c, **13c**: R = $(CH_2)_8Me$ **12g**, **13g**: R = $(CH_2)_{15}Me$
12d, **13d**: R = $(CH_2)_9Me$ **12h**, **13h**: R = $(CH_2)_{17}Me$

Scheme 2. Synthesis of the 3-*epi*-jaspine B analogues bearing 2-alkyloxymethyl group **13a–h**

All anticancer activities of the compounds prepared in the current study were tested against several cancer cell lines, including EC-9706 (human esophageal cancer cells), Eca-109 (human esophageal cancer cells),

B16-F10 (murine melanoma cells) and MCF-7 (human breast cancer cells) cells using an in vitro MTT-based assay over 72 h. The results were compared with jaspine B, which was also evaluated under the same conditions as a positive control.

The results of the MMT assay were summarized in Table 1 for the anticancer activities of the different jaspine B analogues. As shown in Table 1, the jaspine B analogues bearing 2-alkyloxymethyl group with a short side-chain (e.g., **9a**, **9b**, **13a** and **13b**) showed no cytotoxicity against any of all four cell lines tested in the current study. Increasing the length of the carbon chain led to an increase in the cytotoxicity of the compounds against all four cancer cell lines. Compound **9g** bearing a side chain containing 16 carbon atoms showed the most potent cytotoxicity against B16-F10 with IC_{50} values of 2.0 μM. Compound **9h**, which had a longer side chain than **9g**, showed lower levels of cytotoxicity with IC_{50} values of 3.43 μM against the same cell lines, suggesting that when the length of side chain above a certain length, it is unfavorable for the cytotoxicity. Compounds **13a–h** behaved in a similar manner to compounds **9a–h** in the sense that the cytotoxicity of these compounds increased with increasing chain length. Compound **13e** with the same side chain length as jaspine B, was with little lower cytotoxicity ranging from 12.85 to 65.76 μM than jaspine B, indicating that the oxygen atom would not have contributed to the cytotoxicity. Compound **13f** exhibited the most potent cytotoxicity against MCF-7 with IC_{50} values of 2.5 μM. Further increasing the length of the alkyl chain in this series gave compounds **13g** and **13h**, which generally showed reduced cytotoxicity compared with compound **13f**. Furthermore, most of the compounds exhibited higher levels of cytotoxic activity towards B16-F10 and MCF-7 cells than another two cell lines.

Table 1. Primary in vitro anticancer activities of the jaspine B analogues bearing 2-alkyloxymethyl group **9a–h** and **13a–h** against four different cancer cell lines

Compound	R	IC_{50} (μM)[a]			
		Eca109	Ec9706	B16-F10	MCF-7
9a	$Me(CH_2)_6$	>120	>120	>120	>120
9b	$Me(CH_2)_7$	>120	>120	>120	>120
9c	$Me(CH_2)_8$	>120	78.71±5.0	25.20±3.1	117.20±5.7
9d	$Me(CH_2)_9$	53.53±4.2	48.93±4.1	10.87±1.7	41.13±3.8
9e	$Me(CH_2)_{11}$	29.12±3.1	26.27±3.0	6.55±0.9	22.39±2.8
9f	$Me(CH_2)_{13}$	16.45±2.2	21.00±2.5	4.88±0.6	15.81±2.2
9g	$Me(CH_2)_{15}$	17.01±2.2	20.05±2.4	2.0±0.4	6.22±1.0
9h	$Me(CH_2)_{17}$	13.33±1.8	26.24±2.6	3.43±0.3	15.94±2.0
13a	$Me(CH_2)_6$	>120	>120	>120	>120
13b	$Me(CH_2)_7$	>120	>120	>120	>120

13c	$Me(CH_2)_8$	119.23±5.7	113.55±5.7	28.52±3.4	40.20±3.7
13d	$Me(CH_2)_9$	61.10±4.5	33.96±3.5	25.62±3.1	18.62±2.6
13e	$Me(CH_2)_{11}$	19.05±2.5	26.60±3.0	12.85±1.7	65.76±4.3
13f	$Me(CH_2)_{13}$	28.38±2.8	28.69±3.0	10.89±1.7	2.5±0.1
13g	$Me(CH_2)_{15}$	35.10±3.1	44.81±3.3	4.55±0.6	7.76±2.8
13h	$Me(CH_2)_{17}$	62.70±2.6	35.48±3.0	13.70±1.9	26.46±2.6
jaspine B		15.63±2.2	31.39±0.9	5.08±0.6	8.24±1.3

[a]Inhibitory activity was assayed by exposure for 72 h to substances and expressed as concentration required to inhibit tumor cell proliferation by 50% (IC_{50}). Data are presented as the means SDs of three independent experiments.

CONCLUSIONS

In summary, we have designed and synthesized two new series of jaspine B analogues bearing 2-alkyloxymethyl group using a highly efficient method and evaluated their antitumor activities against four cancer cell lines using an MTT-based assay. The cytotoxicity results for these compounds showed that some of them exhibited similar or greater antitumor activities than jaspine B against EC-9706, Eca-109, B16-F10 and MCF-7 cells. Compounds **9g** and **13f**, in particular, were found to be the most promising analogues with cytotoxic activities 2- to 3-fold more potent than those of jaspine B. The results of a structure–activity relationship study showed the length of the side chain and the presence of an oxygen atom were cri have an effect on cytotoxic activity of these compounds.

EXPERIMENTAL

Reagents and solvents were purchased from commercial sources and used without further purification, unless otherwise stated. Reactions were monitored using thin-layer chromatography (TLC) on silica gel plates. Flash column chromatography was performed on silica gel (200-300 mesh) for purification of the compounds. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer at 400 MHz and 100 MHz, respectively. Chemical shift values were reported as δ ppm relative to TMS as internal standard. High resolution mass spectra (HRMS) were recorded on a Waters Micromass Q-T of Micromass spectrometer.

Procedure for the synthesis of ((2S,3S,4S)-4-azido-3-(benzyloxy)tetrahydrofuran-2-yl)methanol (7): To a solution of compound **6** (1.10 g, 4.45 mmol) in EtOH (30 mL) was added KBH_4 (360 mg, 6.67 mmol) at 0 ºC, the mixture was stirred at room temperature for 3 h, then quenched by addition of saturated aqueous NH_4Cl solution. The mixture was evaporated and the residue was extracted with EtOAc, the organic layer was washed with brine, dried, and concentrated to give pure **7** (943 mg, 85% yield) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.47 - 7.33 (m, 5H), 4.84 (d, J = 11.6 Hz, 1H), 4.59 (d,

J = 11.6 Hz, 1H), 4.37 - 4.28 (m, 1H), 4.08 (d, *J* = 5.5 Hz, 1H), 3.99 (dd, *J* = 9.7, 6.1 Hz, 2H), 3.95 - 3.90 (m, 1H), 3.84 (d, *J* = 4.0 Hz, 2H), 2.31 (s, 1H). ^{13}C NMR (100 MHz, CDCl3, ppm): δ 136.98, 128.71, 128.33, 127.94, 79.95, 79.56, 73.86, 69.38, 61.83, 61.22. HRMS (ESI): calcd for $C_{12}H_{15}N_3O_3Na$ $[M+Na]^+$: 272.1108, found: 272.1110.

General procedure for the synthesis of compounds 8a-8h: To a solution of compound **7** (284 mg, 1 mmol) in anhydrous DMF was added sodium hydride (60 mg, 2.5 mmol) at 0 ºC under N_2 atmosphere, stirring at 0 ºC for 1.5 h, followed by adding alkyl bromide (2 mmol). The mixture was stirred at room temperature for 12 h, then added equal volume of water, extracted three times with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo followed by purification by flash column chromatography to yield the pure product.

(2*S*,3*S*,4*S*)-4-Azido-3-(benzyloxy)-2-((heptyloxy)methyl)tetrahydrofuran (8a): Yield: 60%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.42 - 7.29 (m, 5H), 4.79 (d, *J* = 11.6 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.22 (t, *J* = 5.2 Hz, 1H), 4.12 (dt, *J* = 6.8, 5.3 Hz, 1H), 3.98 - 3.92 (m, 2H), 3.87 (dd, *J* = 11.2, 5.8 Hz, 1H), 3.64 (qd, *J* = 10.2, 6.1 Hz, 2H), 3.54 - 3.36 (m, 2H), 1.62 - 1.51 (m, 2H), 1.30 (dd, *J* = 11.8, 6.2 Hz, 8H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.48, 128.49, 128.00, 127.86, 79.53, 79.48, 73.84, 71.80, 69.28, 68.92, 61.28, 31.82, 29.71, 29.17, 26.10, 22.62, 14.10. HRMS: calcd for $C_{19}H_{29}N_3O_3Na$ $[M+Na]^+$: 370.2209, found: 370.2207.

(2*S*,3*S*,4*S*)-4-Azido-3-(benzyloxy)-2-((octyloxy)methyl)tetrahydrofuran (8b): Yield: 60%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.42 - 7.27 (m, 5H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.21 (t, *J* = 5.2 Hz, 1H), 4.11 (dt, *J* = 6.7, 5.3 Hz, 1H), 3.94 (dd, *J* = 6.0, 2.8 Hz, 2H), 3.89 - 3.83 (m, 1H), 3.63 (t, *J* = 5.9 Hz, 2H), 3.54 - 3.35 (m, 2H), 1.71 - 1.39 (m, 2H), 1.27 (d, *J* = 4.9 Hz, 10H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.48, 128.50, 128.00, 127.87, 79.53, 79.48, 73.84, 71.81, 69.29, 68.93, 61.28, 31.84, 29.71, 29.47, 29.27, 26.14, 22.67, 14.12. HRMS: calcd for $C_{19}H_{29}N_3O_3Na$ $[M+Na]^+$: 384.2365, found: 385.2364.

(2*S*,3*S*,4*S*)-4-Azido-3-(benzyloxy)-2-((nonyloxy)methyl)tetrahydrofuran (8c): Yield: 62%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.44 - 7.28 (m, 5H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.21 (t, *J* = 5.2 Hz, 1H), 4.11 (dt, *J* = 6.7, 5.3 Hz, 1H), 3.94 (dd, *J* = 6.0, 2.9 Hz, 2H), 3.89 - 3.83 (m, 1H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.53 - 3.36 (m, 2H), 1.63 - 1.51 (m, 2H), 1.26 (s, 12H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 137.49, 128.49, 128.00, 127.87, 79.53, 79.48, 73.84, 71.81, 69.28, 68.92, 61.28, 31.90, 29.71, 29.57, 29.52, 29.29, 26.14, 22.69, 14.13. HRMS: calcd for $C_{21}H_{33}N_3O_3Na$ $[M+Na]^+$: 398.2522, found: 398.2523.

(2*S*,3*S*,4*S*)-4-Azido-3-(benzyloxy)-2-((decyloxy)methyl)tetrahydrofuran (8d): Yield: 65%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.40 - 7.30 (m, 5H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.21 (t, *J* = 5.2 Hz, 1H), 4.11 (dt, *J* = 10.7, 5.3 Hz, 1H), 3.94 (dd, *J* = 6.0, 2.8 Hz, 2H),

3.90 - 3.82 (m, 1H), 3.63 (t, *J* = 5.9 Hz, 2H), 3.44 (ddd, *J* = 16.2, 9.3, 2.4 Hz, 2H), 1.60 - 1.53 (m, 2H), 1.28 (d, *J* = 23.4 Hz, 14H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 137.48, 128.50, 128.00, 127.87, 79.53, 79.48, 73.85, 71.81, 69.28, 68.92, 61.28, 31.92, 29.71, 29.61, 29.59, 29.52, 29.34, 26.14, 22.70, 14.14. HRMS: calcd for $C_{22}H_{35+}N_3O_3Na$ $[M+Na]^+$: 412.2678, found: 412.2670.

(2*S*,3*S*,4*S*)-4-Azido-3-(benzyloxy)-2-((dodecyloxy)methyl)tetrahydrofuran (8e): Yield: 68%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.41 - 7.28 (m, 5H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.21 (t, *J* = 5.2 Hz, 1H), 4.11 (dt, *J* = 6.8, 5.3 Hz, 1H), 3.94 (dd, *J* = 6.0, 2.6 Hz, 2H), 3.90 - 3.82 (m, 1H), 3.63 (t, *J* = 5.9 Hz, 2H), 3.53 - 3.31 (m, 2H), 1.60 - 1.51 (m, 2H), 1.27 (d, *J* = 11.1 Hz, 18H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.48, 128.50, 128.00, 127.87, 79.53, 79.48, 73.84, 71.81, 69.28, 68.92, 61.28, 31.94, 29.71, 29.69, 29.65, 29.63, 29.62, 29.52, 29.37, 26.15, 22.71, 14.14. HRMS: calcd for $C_{24}H_{39}N_3O_3Na$ $[M+Na]^+$: 440.2991, found: 440.2999.

(2*S*,3*S*,4*S*)-4-Azido-3-(benzyloxy)-2-((tetradecyloxy)methyl)tetrahydrofuran (8f): Yield: 70%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.40 - 7.31 (m, 5H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.21 (t, *J* = 5.2 Hz, 1H), 4.11 (dt, *J* = 10.7, 5.3 Hz, 1H), 3.94 (dd, *J* = 6.0, 2.7 Hz, 21H), 3.89 - 3.84 (m, 1H), 3.63 (t, *J* = 5.9 Hz, 2H), 3.52 - 3.36 (m, 2H), 1.60 - 1.52 (m, 2H), 1.25 (s, 22H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.48, 128.49, 128.00, 127.87, 79.53, 79.48, 73.85, 71.81, 69.28, 68.92, 61.28, 31.94, 29.71, 29.70, 29.69, 29.68, 29.64, 29.62, 29.52, 29.38, 26.15, 22.71, 14.14. HRMS: calcd for $C_{26}H_{43}N_3O_3Na$ $[M+Na]^+$: 468.3304, found: 468.3305.

(2*S*,3*S*,4*S*)-4-Azido-3-(benzyloxy)-2-((hexadecyloxy)methyl)tetrahydrofuran (8g): Yield: 75%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.47 - 7.33 (m, 5H), 4.81 (d, *J* = 11.6 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.24 (t, *J* = 5.2 Hz, 1H), 4.14 (dt, *J* = 6.8, 5.3 Hz, 1H), 3.97 (dd, *J* = 6.0, 2.5 Hz, 2H), 3.89 (dd, *J* = 11.2, 5.8 Hz, 1H), 3.72 - 3.59 (m, 2H), 3.47 (ddd, *J* = 16.1, 9.3, 2.5 Hz, 2H), 1.60 (dd, *J* = 13.0, 6.0 Hz, 2H), 1.28 (s, 26H), 0.91 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.48, 128.50, 128.00, 127.87, 79.52, 79.48, 73.84, 71.82, 69.28, 68.92, 61.28, 31.94, 29.71, 29.64, 29.62, 29.52, 29.38, 26.15, 22.71, 14.14. HRMS: calcd for $C_{28}H_{47}N_3O_3Na$ $[M+Na]^+$: 496.3617, found: 496.36015.

(2*S*,3*S*,4*S*)-4-Azido-3-(benzyloxy)-2-((octadecyloxy)methyl)tetrahydrofuran (8h): Yield: 80%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.47 - 7.29 (m, 5H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.21 (t, *J* = 5.2 Hz, 1H), 4.12 (dd, *J* = 6.9, 5.3 Hz, 1H), 3.95 (dd, *J* = 6.0, 2.5 Hz, 2H), 3.90 - 3.81 (m, 1H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.44 (ddd, *J* = 16.1, 9.2, 2.4 Hz, 2H), 1.63 - 1.46 (m, 2H), 1.25 (s, 30H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.48, 128.49, 128.00, 127.87, 79.53, 79.48, 73.85, 71.82, 69.28, 68.92, 61.28, 31.95, 29.72, 29.64, 29.62, 29.53, 29.38, 26.15, 22.71, 14.14. HRMS: calcd for $C_{30}H_{51}N_3O_3Na$ $[M+Na]^+$: 524.3903, found: 524.3909.

General procedure for the synthesis of compounds 9a-9h: To a solution of compound **8a-8h** (5 mmol) in MeOH (100 mL) containing 1% HCl (v/v) was added Pd/C (10% content, 110 mg), the solution was

bubbled into hydrogenation apparatus and reacted at 60 ºC and 60 psi pressure for about 3 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified on a silica gel column (EtOAc: MeOH: NH_4OH = 13: 1: 0.1) to give pure **9a-9h**.

(2*S*,3*S*,4*S*)-4-Amino-2-((heptyloxy)methyl)tetrahydrofuran-3-ol (9a): Yield: 70%. yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.16 (t, *J* = 5.0 Hz, 1H), 4.03 (dd, *J* = 8.9, 4.6 Hz, 1H), 3.94 (dd, *J* = 8.5, 6.7 Hz, 1H), 3.75 (dd, *J* = 10.5, 3.9 Hz, 1H), 3.69 (dd, *J* = 10.6, 4.8 Hz, 1H), 3.66 - 3.60 (m, 1H), 3.60 - 3.55 (m, 1H), 3.50 (t, *J* = 6.8 Hz, 2H), 2.73 (s, 3H), 1.67 - 1.56 (m, 2H), 1.38 - 1.13 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 80.22, 72.35, 72.31, 72.11, 70.03, 54.45, 31.76, 29.56, 29.10, 26.01, 22.59, 14.08. HRMS: calcd for $C_{12}H_{26}NO_3$ $[M+H]^+$: 232.1834, found: 232.1832.

(2*S*,3*S*,4*S*)-4-Amino-2-((octyloxy)methyl)tetrahydrofuran-3-ol (9b): Yield: 71%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.13 (t, *J* = 4.9 Hz, 1H), 4.02 (dd, *J* = 8.8, 4.7 Hz, 1H), 3.93 (dd, *J* = 8.4, 6.5 Hz, 1H), 3.76 (dd, *J* = 10.6, 3.9 Hz, 1H), 3.69 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.61 (dd, *J* = 8.3, 6.8 Hz, 1H), 3.58 - 3.53 (m, 1H), 3.50 (t, *J* = 6.8 Hz, 2H), 1.71 - 1.51 (m, 2H), 1.29 (dd, *J* = 13.1, 5.9 Hz, 12H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 80.28, 72.56, 72.52, 72.13, 70.14, 54.60, 31.82, 29.58, 29.41, 29.23, 26.08, 22.66, 14.11. HRMS: calcd for $C_{13}H_{28}NO_3$ $[M+H]^+$: 246.1991, found: 246.1992.

(2*S*,3*S*,4*S*)-4-Amino-2-((nonyloxy)methyl)tetrahydrofuran-3-ol (9c): Yield: 71%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.11 (t, *J* = 4.8 Hz, 1H), 4.02 (dd, *J* = 9.0, 4.6 Hz, 1H), 3.93 (dd, *J* = 8.2, 6.6 Hz, 1H), 3.76 (dd, *J* = 10.5, 3.9 Hz, 1H), 3.68 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.63 - 3.57 (m, 1H), 3.57 - 3.52 (m, 1H), 3.49 (t, *J* = 6.8 Hz, 2H), 1.66 - 1.56 (m, 2H), 1.37 - 1.21 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 80.33, 72.56, 72.47, 72.09, 70.12, 54.63, 31.86, 29.58, 29.51, 29.44, 29.25, 26.06, 22.66, 14.10. HRMS: calcd for $C_{13}H_{28}NO_3$ $[M+H]^+$: 260.2147, found: 260.2148.

(2*S*,3*S*,4*S*)-4-Amino-2-((decyloxy)methyl)tetrahydrofuran-3-ol (9d): Yield: 75%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.19 (t, *J* = 4.5 Hz, 1H), 4.04 (dd, *J* = 8.9, 4.5 Hz, 1H), 3.98 - 3.90 (m, 1H), 3.75 (dd, *J* = 10.4, 3.7 Hz, 1H), 3.69 (dd, *J* = 10.4, 4.3 Hz, 1H), 3.66 - 3.61 (m, 1H), 3.58 (d, *J* = 7.7 Hz, 1H), 3.50 (t, *J* = 6.7 Hz, 2H), 1.67 - 1.56 (m, 2H), 1.26 (s, 14H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 80.15, 72.29, 72.27, 72.14, 69.99, 54.35, 31.90, 29.56, 29.50, 29.45, 29.32, 26.06, 22.68, 14.12. HRMS: calcd for $C_{14}H_{30}NO_3$ $[M+H]^+$: 274.2304, found: 274.2314.

(2*S*,3*S*,4*S*)-4-Amino-2-((dodecyloxy)methyl)tetrahydrofuran-3-ol (9e): Yield: 74%. Yellow oil. ^{1}H NMR (400 MHz, CDCl3, ppm): δ 4.13 (t, *J* = 4.8 Hz, 1H), 4.02 (dd, *J* = 8.8, 4.6 Hz, 1H), 3.93 (dd, *J* = 8.2, 6.6 Hz, 1H), 3.76 (dd, *J* = 10.5, 3.9 Hz, 1H), 3.69 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.65 - 3.58 (m, 1H), 3.58 - 3.53 (m, 1H), 3.49 (t, *J* = 6.8 Hz, 2H), 1.66 - 1.55 (m, 2H), 1.25 (s, 18H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 80.28, 72.51, 72.50, 72.13, 70.13, 54.59, 31.92, 29.66, 29.64, 29.61, 29.58, 29.46, 29.36, 26.08, 22.70, 14.13. HRMS: calcd for $C_{16}H_{34}NO_3$ $[M+H]^+$: 302.2617, found:

302.2623.

(2*S*,3*S*,4*S*)-4-Amino-2-((tetradecyloxy)methyl)tetrahydrofuran-3-ol (9f): Yield: 80%. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.19 (t, *J* = 4.8 Hz, 1H), 4.04 (dd, *J* = 8.8, 4.6 Hz, 1H), 3.92 (dd, *J* = 8.2, 6.6 Hz, 1H), 3.76 (dd, *J* = 10.5, 3.9 Hz, 1H), 3.69 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.65 - 3.58 (m, 1H), 3.58 - 3.53 (m, 1H), 3.49 (t, *J* = 6.8 Hz, 2H), 1.60 - 1.52 (m, 2H), 1.25 (s, 22H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 80.28, 72.51, 72.50, 72.13, 70.13, 54.59, 31.92, 29.66, 29.64, 29.61, 29.58, 29.46, 29.36, 26.08, 22.70, 14.13. HRMS: calcd for $C_{18}H_{38}NO_3$ $[M+H]^+$: 330.2930, found: 330.2933.

(2*S*,3*S*,4*S*)-4-Amino-2-((hexadecyloxy)methyl)tetrahydrofuran-3-ol (9g): Yield: 78%. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.16 (s, 1H), 4.04 (dd, *J* = 8.7, 4.4 Hz, 1H), 3.96 (dd, *J* = 11.6, 6.4 Hz, 1H), 3.78 (dd, *J* = 10.5, 3.8 Hz, 1H), 3.71 (dd, *J* = 10.6, 4.7 Hz, 1H), 3.64 (dd, *J* = 8.9, 4.3 Hz, 1H), 3.61 - 3.56 (m, 1H), 3.52 (t, *J* = 6.8 Hz, 2H), 1.61 (d, *J* = 7.1 Hz, 2H), 1.43 - 1.24 (m, 26H), 0.90 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 80.24, 72.50, 72.49, 72.15, 70.10, 54.55, 31.93, 29.69, 29.66, 29.61, 29.45, 29.36, 26.07, 22.69, 14.11. HRMS: calcd for $C_{20}H_{42}NO_3$ $[M+H]^+$: 358.3243, found: 358.3229.

(2*S*,3*S*,4*S*)-4-Amino-2-((octadecyloxy)methyl)tetrahydrofuran-3-ol (9h): Yield: 80%. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.12 (t, *J* = 4.9 Hz, 1H), 4.02 (dd, *J* = 8.8, 4.7 Hz, 1H), 3.93 (dd, *J* = 8.3, 6.5 Hz, 1H), 3.76 (dd, *J* = 10.6, 3.9 Hz, 1H), 3.69 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.60 (dd, *J* = 8.2, 6.9 Hz, 1H), 3.57 - 3.52 (m, 1H), 3.49 (t, *J* = 6.8 Hz, 2H), 1.70 - 1.53 (m, 2H), 1.29 (d, *J* = 33.0 Hz, 30H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 80.31, 72.59, 72.54, 72.13, 70.14, 54.62, 31.93, 29.71, 29.67, 29.62, 29.59, 29.46, 29.37, 26.08, 22.70, 14.13. HRMS: calcd for $C_{22}H_{46}NO_3$ $[M+H]^+$: 386.3556, found: 386.3567.

Procedure for the synthesis of ((2R,3R,4S)-4-Azido-3-(benzyloxy)tetrahydrofuran-2-yl)methanol (11): The procedure for the synthesis of compound **11** was the same as compound **7**. Yield: 91%. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.41 - 7.29 (m, 5H), 4.60 (q, *J* = 11.7 Hz, 2H), 4.06 - 3.98 (m, 2H), 3.98 - 3.88 (m, 3H), 3.83 - 3.75 (m, 1H), 3.65 (ddd, *J* = 11.8, 6.9, 5.0 Hz, 1H), 2.25 (d, *J* = 5.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.1, 128.6, 128.20, 127.87, 84.84, 84.20, 72.54, 71.03, 65.94, 62.33.

General procedure for the synthesis of compounds 12a-12h: The procedure for the synthesis of compounds **8a-8h** was the same as compounds **12a-12h**.

(2*R*,3*R*,4*S*)-4-Azido-3-(benzyloxy)-2-((heptyloxy)methyl)tetrahydrofuran (12a): Yield: 65%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.45 - 7.30 (m, 5H), 4.65 (d, *J* = 11.8 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.09 - 3.95 (m, 4H), 3.93 (d, *J* = 4.3 Hz, 1H), 3.55 (dd, *J* = 5.4, 0.9 Hz, 2H), 3.48 (td, *J* = 6.7, 1.8 Hz, 2H), 1.61 (dd, *J* = 12.2, 5.1 Hz, 2H), 1.31 (d, *J* = 5.9 Hz, 8H), 0.91 (t, *J* = 6.8 Hz, 3H). ^{13}C

NMR (101 MHz, $CDCl_3$, ppm): δ 128.55, 128.06, 127.86, 84.95, 83.31, 72.26, 71.88, 70.88, 70.62, 65.81, 31.82, 29.62, 29.16, 26.07, 22.63, 14.10. HRMS: calcd for $C_{19}H_{29}N_3O_3Na$ $[M+Na]^+$: 370.2209, found: 370.2207.

(2*R*,3*R*,4*S*)-4-Azido-3-(benzyloxy)-2-((octyloxy)methyl)tetrahydrofuran (12b): Yield: 68%. Light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.46 - 7.31 (m, 5H), 4.65 (d, *J* = 11.8 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.07 - 3.96 (m, 4H), 3.94 (d, *J* = 4.2 Hz, 1H), 3.56 (dd, *J* = 5.4, 1.3 Hz, 2H), 3.48 (td, *J* = 6.7, 1.7 Hz, 2H), 1.67 - 1.55 (m, 2H), 1.33 (d, *J* = 18.4 Hz, 10H), 0.91 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.33, 128.55, 128.05, 127.86, 84.96, 83.31, 72.26, 71.88, 70.87, 70.63, 65.82, 31.84, 29.62, 29.45, 29.27, 26.12, 22.67, 14.10. HRMS: calcd for $C_{19}H_{29}N_3O_3Na$ $[M+Na]^+$: 384.2365, found: 385.2364.

(2*R*,3*R*,4*S*)-4-Azido-3-(benzyloxy)-2-((nonyloxy)methyl)tetrahydrofuran (12c): Yield: 70%. Light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.43 - 7.31 (m, 5H), 4.65 (d, *J* = 11.8 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.07 - 3.95 (m, 4H), 3.94 (d, *J* = 4.2 Hz, 1H), 3.56 (dd, *J* = 5.4, 1.3 Hz, 2H), 3.48 (td, *J* = 6.7, 1.7 Hz, 2H), 1.65 - 1.53 (m, 2H), 1.30 (s, 12H), 0.91 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.33, 128.55, 128.05, 127.86, 84.96, 83.31, 72.26, 71.88, 70.87, 70.62, 65.82, 31.90, 29.62, 29.58, 29.50, 29.29, 26.12, 22.69, 14.12. HRMS: calcd for $C_{21}H_{33}N_3O_3Na$ $[M+Na]^+$: 398.2522, found: 398.2523.

(2*R*,3*R*,4*S*)-4-Azido-3-(benzyloxy)-2-((decyloxy)methyl)tetrahydrofuran (12d): Yield: 70%. Light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.45 - 7.31 (m, 5H), 4.65 (d, *J* = 11.8 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.08 - 3.96 (m, 4H), 3.94 (dd, *J* = 4.2, 1.2 Hz, 1H), 3.56 (dd, *J* = 5.4, 1.4 Hz, 2H), 3.48 (td, *J* = 6.7, 1.7 Hz, 2H), 1.64 - 1.56 (m, 2H), 1.30 (s, 14H), 0.91 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 137.33, 128.55, 128.05, 127.86, 84.96, 83.31, 72.26, 71.88, 70.87, 70.62, 65.82, 31.92, 29.62, 29.60, 29.50, 29.35, 26.12, 22.70, 14.12. HRMS: calcd for $C_{22}H_{35+}N_3O_3Na$ $[M+Na]^+$: 412.2678, found: 412.2670.

(2*R*,3*R*,4*S*)-4-Azido-3-(benzyloxy)-2-((dodecyloxy)methyl)tetrahydrofuran (12e): Yield: 75%. Light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.42 - 7.27 (m, 5H), 4.62 (d, *J* = 11.8 Hz, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.03 - 3.92 (m, 4H), 3.90 (d, *J* = 4.3 Hz, 1H), 3.52 (dd, *J* = 5.4, 1.1 Hz, 2H), 3.45 (td, *J* = 6.7, 1.6 Hz, 2H), 1.56 (d, *J* = 7.0 Hz, 2H), 1.26 (s, 18H), 0.88 (t, *J* = 6.8 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.33, 128.54, 128.05, 127.86, 84.96, 83.30, 72.25, 71.88, 70.87, 70.62, 65.82, 31.94, 29.69, 29.66, 29.64, 29.63, 29.51, 29.37, 26.12, 22.70, 14.13. HRMS: calcd for $C_{24}H_{39}N_3O_3Na$ $[M+Na]^+$: 440.2991, found: 440.2999.

(2*R*,3*R*,4*S*)-4-Azido-3-(benzyloxy)-2((tetradecyloxy)methyl)tetrahydrofuran (12f): Yield: 75%. Light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.42 - 7.31 (m, 5H), 4.65 (d, *J* = 11.8 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.07 - 3.96 (m, 4H), 3.94 (dd, *J* = 4.3, 1.3 Hz, 1H), 3.56 (dd, *J* = 5.4, 1.9 Hz, 2H), 3.48

(td, *J* = 6.7, 1.5 Hz, 2H), 1.65 - 1.57 (m, 2H), 1.29 (s, 22H), 0.92 (t, *J* = 6.8 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.34, 128.53, 128.03, 127.85, 84.97, 83.31, 72.25, 71.88, 70.85, 70.63, 65.84, 31.94, 29.71, 29.69, 29.67, 29.63, 29.50, 29.37, 26.12, 22.70, 14.11. HRMS: calcd for $C_{26}H_{43}N_3O_3Na$ $[M+Na]^+$: 468.3304, found: 468.3305.

(2*R*,3*R*,4*S*)-4-Azido-3-(benzyloxy)-2((hexadecyloxy)methyl)tetrahydrofuran (12g): Yield: 80%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.41 - 7.28 (m, 5H), 4.63 (d, *J* = 11.8 Hz, 1H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.04 - 3.93 (m, 4H), 3.91 (d, *J* = 4.3 Hz, 1H), 3.53 (dd, *J* = 5.4, 1.2 Hz, 2H), 3.45 (td, *J* = 6.7, 1.7 Hz, 2H), 1.62 - 1.54 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 26H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.33, 128.54, 128.04, 127.86, 84.96, 83.31, 72.25, 71.88, 70.86, 70.62, 65.82, 31.95, 29.72, 29.68, 29.65, 29.63, 29.51, 29.38, 26.13, 22.71, 14.13. HRMS: calcd for $C_{28}H_{47}N_3O_3Na$ $[M+Na]^+$: 496.3617, found: 496.3615.

(2*R*,3*R*,4*S*)-4-Azido-3-(benzyloxy)-2-((octadecyloxy)methyl)tetrahydrofuran (12h): Yield: 70%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.47 - 7.30 (m, 5H), 4.71 - 4.53 (m, 2H), 4.07 - 3.95 (m, 4H), 3.94 (d, *J* = 4.3 Hz, 1H), 3.56 (dd, *J* = 5.4, 1.3 Hz, 2H), 3.48 (td, *J* = 6.7, 1.6 Hz, 2H), 1.62 - 1.55 (m, 2H), 1.29 (s, 30H), 0.91 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.33, 128.54, 128.04, 127.86, 84.96, 83.30, 72.26, 71.89, 70.87, 70.62, 65.82, 31.94, 29.72, 29.68, 29.65, 29.63, 29.51, 29.38, 26.12, 22.71, 14.13. HRMS: calcd for $C_{30}H_{51}N_3O_3Na$ $[M+Na]^+$: 524.3903, found: 524.3909.

General procedure for the synthesis of compounds 13a-13h: The procedure for the synthesis of compounds **13a-13h** was the same as compounds **9a-9h**.

(2*R*,3*R*,4*S*)-4-Amino-2-((heptyloxy)methyl)tetrahydrofuran-3-ol (13a): Yield: 90%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.04 (dd, *J* = 9.2, 5.0 Hz, 1H), 3.97 - 3.89 (m, 1H), 3.83 (dd, *J* = 7.7, 4.0 Hz, 1H), 3.68 - 3.62 (m, 2H), 3.59 (dd, *J* = 10.4, 4.1 Hz, 1H), 3.55 - 3.39 (m, 2H), 3.32 - 3.24 (m, 1H), 1.66 - 1.52 (m, 2H), 1.35 - 1.18 (m, 8H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 84.64, 79.42, 74.66, 71.97, 70.96, 60.09, 31.77, 29.57, 29.12, 26.03, 22.60, 14.07. HRMS: calcd for $C_{12}H_{26}NO_3$ $[M+H]^+$: 232.1834, found: 232.1832.

(2*R*,3*R*,4*S*)-4-Amino-2-((octyloxy)methyl)tetrahydrofuran-3-ol (13b): Yield: 91%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.03 (ddd, *J* = 9.1, 4.9, 1.8 Hz, 1H), 3.93 (d, *J* = 2.2 Hz, 1H), 3.83 (d, *J* = 3.1 Hz, 1H), 3.69 - 3.64 (m, 1H), 3.64 - 3.61 (m, 1H), 3.60 (dd, *J* = 3.9, 1.9 Hz, 1H), 3.47 (ddd, *J* = 8.9, 8.0, 4.5 Hz, 2H), 3.32 - 3.25 (m, 1H), 1.64 - 1.52 (m, 2H), 1.26 (s, 12H), 0.87 (dd, *J* = 6.8, 5.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 84.70, 79.28, 74.51, 71.97, 70.93, 60.06, 31.81, 29.56, 29.42, 29.23, 26.06, 22.63, 14.08. HRMS: calcd for $C_{13}H_{28}NO_3$ $[M+H]^+$: 246.1991, found: 246.1992.

(2*R*,3*R*,4*S*)-4-Amino-2-((nonyloxy)methyl)tetrahydrofuran-3-ol (13c): Yield: 89%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.04 (dd, *J* = 9.2, 5.1 Hz, 1H), 3.98 - 3.88 (m, 1H), 3.83 (dd, *J* = 7.9, 4.1 Hz, 1H), 3.65 (dd, *J* = 6.3, 2.9 Hz, 1H), 3.63 (d, *J* = 3.5 Hz, 1H), 3.59 (dd, *J* = 10.4, 4.2 Hz, 1H), 3.48

(ddd, *J* = 13.6, 9.3, 2.4 Hz, 2H), 3.33 - 3.20 (m, 1H), 1.67 - 1.52 (m, 2H), 1.26 (s, 12H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 84.68, 79.38, 74.65, 71.97, 70.96, 60.10, 31.85, 29.57, 29.53, 29.47, 29.27, 26.06, 22.65, 14.09. HRMS: calcd for $C_{14}H_{30}NO_3$ $[M+H]^+$: 260.2147, found: 260.2148.

(2*R*,3*R*,4*S*)-4-Amino-2-((decyloxy)methyl)tetrahydrofuran-3-ol (13d): Yield: 89%. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.04 (dd, *J* = 9.2, 5.1 Hz, 1H), 3.97 - 3.86 (m, 1H), 3.83 (q, *J* = 3.8 Hz, 1H), 3.68 - 3.64 (m, 1H), 3.63 (d, *J* = 3.5 Hz, 1H), 3.60 (dd, *J* = 10.3, 4.1 Hz, 1H), 3.56 - 3.39 (m, 2H), 3.28 (dd, *J* = 4.7, 2.9 Hz, 1H), 1.67 - 1.53 (m, 2H), 1.26 (s, 14H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 84.59, 79.72, 74.78, 71.98, 71.02, 60.20, 31.90, 29.59, 29.48, 29.32, 26.10, 22.68, 14.12. HRMS: calcd for $C_{15}H_{32}NO_3$ $[M+H]^+$: 274.2304, found: 274.2314.

(2*R*,3*R*,4*S*)-4-Amino-2-((dodecyloxy)methyl)tetrahydrofuran-3-ol (13e): Yield: 90%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.04 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.97 - 3.88 (m, 1H), 3.82 (dd, *J* = 8.3, 4.1 Hz, 1H), 3.67 - 3.63 (m, 1H), 3.62 (d, *J* = 3.3 Hz, 1H), 3.61 - 3.57 (m, 1H), 3.48 (qt, *J* = 9.3, 6.8 Hz, 2H), 3.29 (dt, *J* = 5.3, 3.3 Hz, 1H), 1.57 (dd, *J* = 14.2, 7.0 Hz, 2H), 1.27 (d, *J* = 9.9 Hz, 18H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 84.52, 79.88, 74.73, 71.99, 71.06, 60.18, 31.92, 29.67, 29.64, 29.60, 29.49, 29.35, 26.10, 22.69, 14.12. HRMS: calcd for $C_{17}H_{36}NO_3$ $[M+H]^+$: 302.2617, found: 302.2623.

(2*R*,3*R*,4*S*)-4-Amino-2-((tetradecyloxy)methyl)tetrahydrofuran-3-ol (13f): Yield: 87%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.06 (dd, *J* = 9.3, 5.0 Hz, 1H), 4.01 - 3.95 (m, 1H), 3.86 (dd, *J* = 7.6, 3.8 Hz, 1H), 3.70 (dd, *J* = 9.3, 3.0 Hz, 1H), 3.63 (qd, *J* = 10.4, 3.6 Hz, 2H), 3.50 (tdd, *J* = 16.2, 9.3, 6.9 Hz, 2H), 3.35 (d, *J* = 2.7 Hz, 1H), 1.73 - 1.49 (m, 2H), 1.28 (d, *J* = 11.2 Hz, 22H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 84.55, 79.32, 74.01, 72.01, 70.96, 59.82, 31.92, 29.69, 29.67, 29.65, 29.60, 29.55, 29.48, 29.35, 26.07, 22.68, 14.10. HRMS: calcd for $C_{19}H_{40}NO_3$ $[M+H]^+$: 330.2930, found: 330.2933.

(2*R*,3*R*,4*S*)-4-Amino-2-((hexadecyloxy)methyl)tetrahydrofuran-3-ol (13g): Yield: 89%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.05 (dd, *J* = 9.4, 5.0 Hz, 1H), 4.02 - 3.95 (m, 1H), 3.85 (dd, *J* = 7.6, 3.8 Hz, 1H), 3.71 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.69 - 3.56 (m, 5H), 3.55 - 3.42 (m, 2H), 3.41 - 3.35 (m, 1H), 1.57 (dd, *J* = 13.8, 6.9 Hz, 2H), 1.27 (d, *J* = 11.2 Hz, 26H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 84.48, 79.29, 73.72, 72.02, 70.96, 59.68, 31.92, 29.70, 29.68, 29.66, 29.64, 29.60, 29.54, 29.48, 29.36, 26.06, 22.69, 14.11. HRMS: calcd for $C_{21}H_{44}NO_3$ $[M+H]^+$: 358.3243, found: 358.3229.

(2*R*,3*R*,4*S*)-4-Amino-2-((octadecyloxy)methyl)tetrahydrofuran-3-ol (13h): Yield: 87%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.06 (dd, *J* = 9.4, 4.9 Hz, 1H), 4.03 - 3.98 (m, 1H), 3.87 (dd, *J* = 7.5, 3.8 Hz, 1H), 3.73 (dd, *J* = 9.2, 2.6 Hz, 4H), 3.66 (dd, *J* = 10.4, 3.2 Hz, 1H), 3.61 (dd, *J* = 10.4, 3.9 Hz, 1H), 3.57 - 3.43 (m, 2H), 3.38 (s, 1H), 1.65 - 1.56 (m, 2H), 1.39 - 1.21 (m, 32H), 0.89 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 84.51, 79.36, 73.94, 72.02, 70.97, 59.78, 31.92, 29.70, 29.66, 29.60, 29.55, 29.48, 29.36, 26.07, 22.68, 14.11. HRMS: calcd for $C_{21}H_{44}NO_3$ $[M+H]^+$: 386.3556, found: 386.3567.

Cytotoxicity assays: In brief, the exponentially growing cells (5×10^3 cells/well) were seeded in 96-well plates filled with RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS) containing various concentrations of samples, and incubated for 72 h. 25 μL of MTT reagent (5 mg/mL) in PBS medium was added to each well and incubated at 37 °C for 4 h. Discarded the suspension and added 150 μL of pure DMSO was added to each well and shook the plates to dissolve the dark blue crystals (formazan). After 15 min of incubation, the readings were recorded as absorbance at 490 nm on a microplate reader, which is directly proportional to the number of living cells in culture. Each concentration was analyzed in triplicate and the experiment was repeated three times. IC_{50} values were calculated according to the dosedependent curves.

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