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# Synthesis and preliminary biological evaluation of 1,2,3-triazole-Jaspine B hybrids as potential cytotoxic agents

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ABSTRACT

Two series of more available novel 1,2,3-triazole-Jaspine B hybrids were efficiently synthesized employing click chemistry approach and evaluated for their cytotoxic activities against three human cancer cell lines (EC-9706, MGC-803 and MCF-7). Among them, compound **14h** showed excellent inhibition against MCF-7 ($IC_{50}$ = 1.93 μM) and was more potent than 5-Fu and Jaspine B against all three cancer cell lines. Further investigation of apoptosis assay and cell cycle analysis demonstrated that compound **14h** caused cellular early and late apoptosis and arrested the cell cycle at G2/M phase in a concentration- and time-independent manner. This was the first report about the synthesis and *in vitro* cytotoxic evaluation of 1,2,3-triazole-Jaspine B hybrids.



## 1. Introduction

Jaspine B (Fig. 1), as the first naturally occurring anhydrophytosphingosine derivative, was isolated from the marine sponge *Pachastrissa* sp. and *Jaspis* sp. This natural Jaspine B was reported to exhibit submicromolar cytotoxicity against various cell lines [1,2]. Moreover, Yahya and co-workers revealed that Jaspine B inhibited sphingomyelin synthase (SMS) and consequently increased intracellular ceramide levels, resulting in apoptosis in tumor cell by a caspase-dependent pathway [3,4]. Fujii and co-workers revealed that Jaspine B and its diastereoisomers inhibited sphingosine kinases (SphKs) and atypical protein kinase C [5,6]. Due to its remarkable bioactivities and structural novelty, much more effort has been devoted to the synthesis of Jaspine B, its stereoisomers and analogues [3,5,7–18].

1, 2, 3-Triazoles, as an important class of heterocycles, display a wide range of biological activities [19–23] and are regarded as the interesting scaffold with significant anticancer profile in many human cell lines [24–27]. 1,2,3-Triazoles could be easily constructed by click chemistry reaction [28], and conferred small molecules with special properties like moderate dipole character, hydrogen bonding capability, rigidity and stability [29]. Recently, multiple series of 1,2,3-triazole derivatives with diverse biological activities have been reported [30–33], and several drug molecules containing 1,2,3-triazole group such as tazobactam [34] and the cephalosporin cefatrizine [35] are examples of antibiotic drugs that are clinically used for the treatment of bacterial infections (Fig. 1). Besides, 1,2,3-triazoles conjugated with other pharmacophores have exhibited potent anticancer activities [36,37]. For example, Kamal recently reported the synthesis of a new class of triazole-chalcone-pyrrolo [2,1-c] [1,4] benzodiazepine (PBD) hybrids, which showed G1 cell cycle arrest and acted as inhibitors of Cyclin D1 and NF-kB protein [38]. Our group recently synthesized novel 1,2,3-triazole-dithiocarbamate hybrids and evaluated their cytotoxic activities, finding some promising candidates with broad spectrum anticancer activities and low cytotoxicity against the normal cell HEK-293. Particularly, some of them were more potent than the well-known anticancer drug 5-fluorouracil [39–41].

Jaspine B has a 2-tetradecanyltetrahydrofuran scaffold with a free amino group and a hydroxyl group. The long alkyl chain was normally introduced through Wittig reaction [10] and Ru-mediated cross-metathesis [42] or from expensive materials [15]. Therefore, the efficient synthesis of long alkyl chains of Jaspine B derivatives via relatively simple reaction is in highly demand. In continuation with our efforts in this area and considering the biological importance of Jaspine B and 1,2,3-triazole derivates as anticancer agents, herein we reported the synthesis of two series of novel 1,2,3-triazole-Jaspine B hybrids with chiral tetrahydrofuran backbone and a

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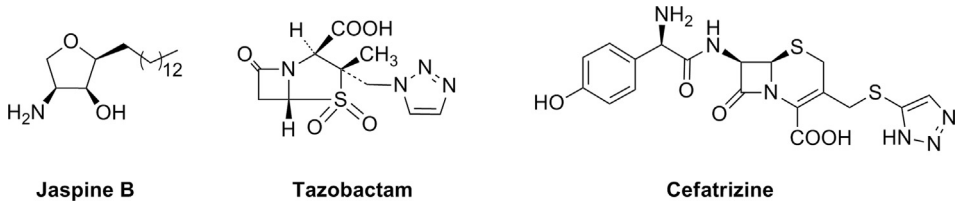



**Fig. 1.** Structures of Jaspine B, Tazobactam and Cefatrizine.

lipophilic alkyl chain (Fig. 2) and further evaluated their cytotoxic activities.

## 2. Results and discussion

### 2.1. Chemistry

Compounds **1** and **7** were synthesized following our previous reported procedure [16].The synthetic route for the 1,2,3-triazole-Jaspine B hybrids is outlined in Scheme 1. The synthetic route started with the reduction of aldehyde **1** using $KBH_4$, giving compound **2**, which was further reacted with propargyl bromide in the presence of NaOH to yield compound **3** in 83% yield. Reduction of **3** under Staudinger reaction condition followed by treatment of the resultant amino group with $(Boc)_2O$ afforded the key intermediate **4**. The alkynyl group of **4** was then subjected to click reaction with various azides having different chain lengths, affording **5** in excellent yield. The azides were efficiently prepared from the corresponding alkyl bromides and sodium azide via $S_N2$ reaction [43]. Pd/C-catalyzed one-pot deprotection of the *N*-Boc and benzyl group of compound **5** under acidic condition provided corresponding compound **6**.

The synthetic route for 1, 2, 3-triazole-3-*epi*-Jaspine B hybrids is outlined in Scheme 2. Benzylation of compound **7** with benzyl bromide in the presence of $K_2CO_3$ in THF under reflux gave compound **8**, which was then treated with 75% TFA in DCM, affording the aldehyde **9** (a diastereomer of compound **1**). Compounds **14** were synthesized from aldehyde **9** according to the corresponding procedure mentioned in Scheme 1.

All the synthesized compounds were fully characterized by $^1H$, $^{13}C$ NMR and high resolution mass spectra as described for compound **6g** (Fig. 3). We have identified H1–H9, H24 and C1–C9, C24 of compound **6g** from 1D NMR ($^1H$ NMR, $^{13}C$ NMR and DEPT135) and 2D NMR (HSQC, COSY and HMBC) of **6g**. The numbers of the hydrogens and carbons corresponding to **6g** were showed below (Fig. 3). From the HSQC spectrum together with $^1H$ and $^{13}C$ NMR spectra, some direct C–H correlations were observed, confirming that the signals of the alkyl chain carbons (C-10 to C-23) appeared at 28.97–31.89 ppm and the alkyl protons appeared at 1.82–1.96, 1.25–1.31. For all the spectra of compound **6g**, please refer to the Supporting Information.

### 2.2. Biological evaluation

#### 2.2.1. Cytotoxic activity

All the synthesized 1,2,3-triazole-Jaspine B hybrids were tested *in vitro* against three human cancer cell lines, including MGC-803 (human gastric cancer cell line), MCF-7 (human breast cancer cell line) and EC-9706 (human esophageal cancer cell line) using the MTT assay and the results were compared with Jaspine B and well-known anticancer drug 5-fluorouracil.

The $IC_{50}$ values of the tested compounds were listed in Table 1. As shown in Table 1, compound **6a** with the shortest side-chain showed no cytotoxicity against all three cells. Compounds (**6b**–**6f**) with prolonged side-chains showed enhanced cytotoxicity. Compound **6f** with alkyl-chain of 14 carbon atoms showed the most potent cytotoxicity against EC-9706, MGC-803 and MCF-7 cells, respectively with the $IC_{50}$ values of 7.83, 8.21 and 1.85 μM. However, compounds **6g** and **6h** with longer alkyl chain than 14 carbons exhibited relatively weak cytotoxicity ranging from 3.30 to 19.99 μM and 7.58–17.89 μM. More clear behavior of 1, 2, 3-triazole-3-*epi*-Jaspine B hybrids **14a**–**14h** was observed against all the tested cancer cells. Compounds with prolonged side-chains showed enhanced cytotoxicity. Specifically, compounds **14a**–**c** showed no cytotoxicity against all the tested cell lines. Compounds **14d** and **14e** showed weak cytotoxicity ranging from 43.10 to 57.39 μM and 2.62–115.08 μM. Compound **14f**, with the same alkyl-chain length as Jaspine B exhibited similar cytotoxicity ranging from 2.45 to 8.79 μM. Compounds **14g** and **14h** with prolonged alkyl chain exhibited better cytotoxicity ranging from 2.26 to 6.32 μM and 1.93–3.11 μM, suggesting that the length of side-chain may play an important role in cytotoxicity. It is worth noting that compound **14h** with the prolonged alkyl chain proved to be nearly 2-fold more potent than Jaspine B in all three cancer cell lines. This is different from compound **6h** that showed moderate cytotoxicity. Besides, most of the compounds were more active to MCF-7 than other two cell lines.

#### 2.2.2. Apoptosis assay

Due to the excellent cytotoxicity of **14h** against all tested human cancer cell lines, it was chosen to be further investigated regarding its mechanism of action. To test whether the inhibition of cell growth was related to cell apoptosis, we performed a biparametric cytofluorimetric analysis of **14h** using propidium iodide (PI) and annexin-V-FITC in MCF-7 cells. After treatment with compound **14h** for 8 or 16 h at different concentrations (0, 2, 4, 8 μM), MCF-7 cells were labeled with the two dyes, and the resulting red (PI) and green (FITC) fluorescence was monitored by flow cytometry. It can be observed from Fig. 4 that compound **14h** caused the early and late apoptosis. Specifically, the early and late apoptosis rates were significantly increased from 8.2% to 6.8% (for the control group) to 23.8% and 18.6%, respectively (for the high concentration group, 8 μM). Similarly, compared with control (11.1% and 0.7%), the early and late apoptosis rates for the high concentration group (8 μM) were 57.9% and 12.5% after treatment for 16 h. The results revealed that **14h** caused a markedly increased the cellular apoptosis in a concentration- and time-independent manner.

#### 2.2.3. Cell cycle analysis

To determine whether the high inhibitory effect of the **14h** were caused by cell cycle accumulation at a certain phase, a cell-cycle cytotoxicity assay was performed by treating MCF-7 cells at different concentrations of compound **14h** (0, 2, 4, 8 μM). After treatment MCF-7 cells for **14h**, it was observed that the percentage of cells in G2/M phase at different concentrations were 19.35%, 27.97%, 30.72% and 39.13%, respectively (Fig. 5A), whereas when treatment for 16 h, the percentage of cells in G2/M phase were 20.08%, 28.6%, 36.4% and 47.4%, respectively (Fig. 5B). These results

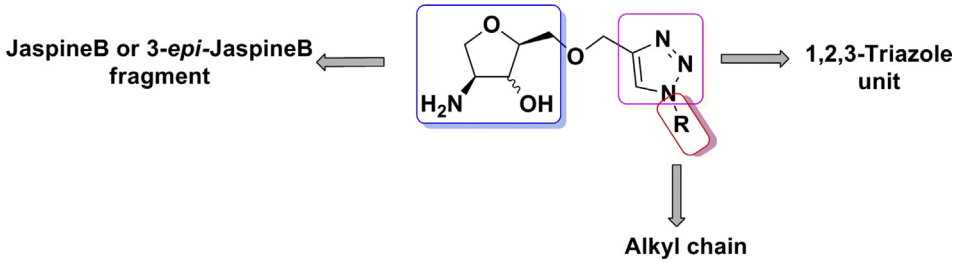
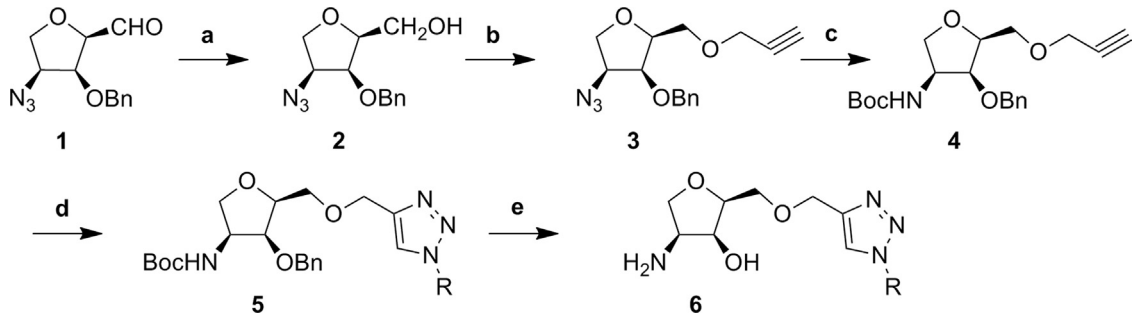
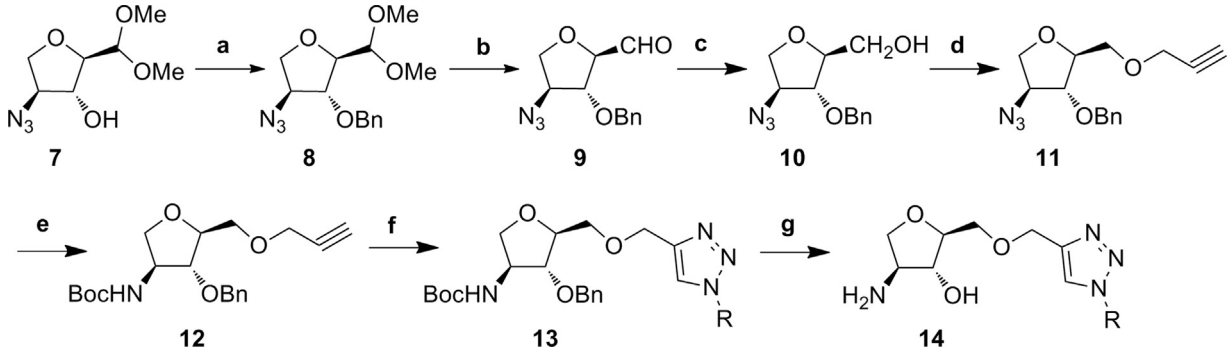



**Fig. 2.** 1,2,3-triazole-Jaspine B hybrids.



**Scheme 1.** Synthesis of the 1,2,3-triazole-Jaspine B hybrids (**6a**–**h**). Reagent and reaction conditions: (a) $KBH_4$, ethanol, rt; (b) propargyl bromide, NaOH, acetonitrile, reflux; (c) (i) $PPh_3$, THF-$H_2O$ (6:1), reflux; (ii) THF, $(Boc)_2O$, rt; (d) alkylazide, $CuSO_4.5H_2O$, sodium ascorbate, THF-$H_2O$ (1:1), rt; (e) 5% Pd/C, $CH_3OH$–HCl, 60 atm, 60 °C.



**Scheme 2.** Synthesis of the 1,2,3-triazole-3-*epi* Jaspine B hybrids (**14a**–**h**). Reagent and reaction conditions: (a) 75% TFA, dichloromethane, 40 °C; (b) BnBr, THF, reflux; (c) $KBH_4$, ethanol, rt; (d) propargyl bromide, NaOH, acetonitrile, reflux; (e) (i) $PPh_3$, THF-$H_2O$ (6:1), reflux; (ii) THF, $(Boc)_2O$, rt; (f) alkylazide, $CuSO_4.5H_2O$, sodium ascorbate, THF-$H_2O$ (1:1), rt; (g) 5% Pd/C, $CH_3OH$–HCl, 60 atm, 60 °C.

suggested that **14h** caused an obvious G2/M arrest in a concentration- and time-dependent manner with a concomitant decrease in terms of the number of cells in the G1 and S phases of the cell cycle.

## 3. Conclusion

In conclusion, two series of 1,2,3-triazole-Jaspine B hybrids were synthesized in high yields and screened for cytotoxic activities against three human cancer cell lines. Compounds **6f**, **14f**, **14g** and **14h** with 1,2,3-triazole side-chain exhibited excellent *in vitro* cytotoxicity. Further investigation of apoptosis assay and cell cycle analysis demonstrated that **14h** caused cellular early and late apoptosis and arrested the cell cycle at G2/M phase in a concentration- and time-independent manner. The results revealed that full carbon alkyl chain of natural Jaspine B was replaced successfully with more available 1,2,3-triazole linked alkyl chain. The side-chain length and 1,2,3-triazole unit had remarkable effects toward their cytotoxicity. Synthesis of more analogs and further mechanism studies are in progress and will be reported in due course.

## 4. Experimental section

### 4.1. General

Reagents and solvents were purchased from commercial sources and were used without further purification. Melting points were determined on an X-5 micromelting apparatus and are uncorrected. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Bruker 400 MHz and 100 MHz spectrometer respectively. High resolution mass spectra (HRMS) were recorded on a Waters Micromass Q-T of Micromass spectrometer.

### 4.2. Procedure for the synthesis of ((2S,3S,4S)-4-azido-3-(benzyloxy)tetrahydrofuran-2-yl)-methanol compound **2**

To a solution of Compound **1** (569 mg, 2 mmol) in ethanol (15 mL) was added $KBH_4$ (184 mg, 3 mmol) under the ice bath. The resultant solution was warmed to room temperature and allowed to react for 5 h. The reaction mixture was quenched by addition of saturated $NH_4Cl$ aqueous solution at 0 °C, and concentrated under

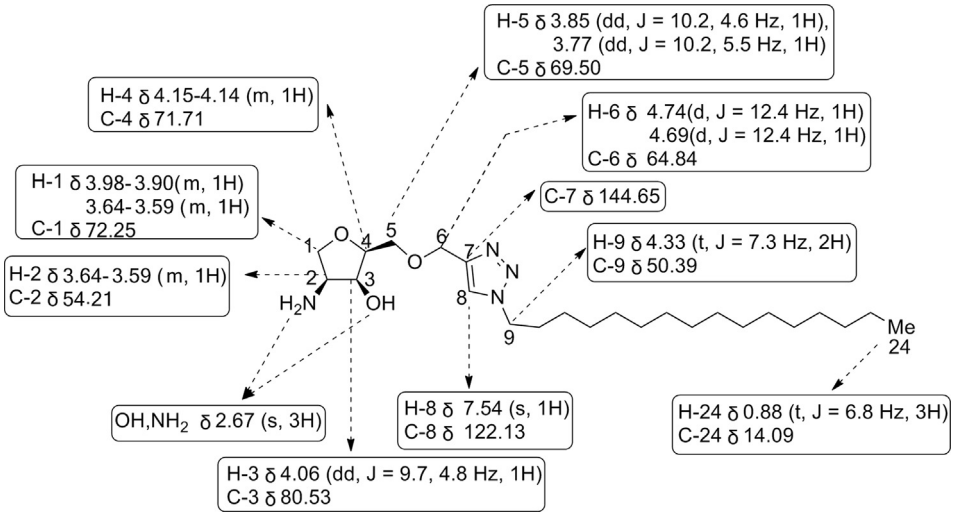



**Fig. 3.** 1H NMR and 13C NMR chemical shifts of compound **6g**.

**Table 1**
Primary *in vitro* anticancer activity of the 1,2,3-triazole-Jaspine B hybrids against three human cancer cell lines.

| Compound | *R* | $IC_{50}(\mu M)$[a] | | |
|---|---|---|---|---|
| | | EC-9706 | MGC-803 | MCF-7 |
| **6a** | $CH_3(CH_2)_6$ | >128 | >128 | >128 |
| **6b** | $CH_3(CH_2)_7$ | 44.27 ± 3.55 | 70.42 ± 4.17 | 28.11 ± 2.95 |
| **6c** | $CH_3(CH_2)_8$ | 20.13 ± 2.46 | 13.81 ± 1.98 | 12.44 ± 1.84 |
| **6d** | $CH_3(CH_2)_9$ | 15.57 ± 2.09 | 8.78 ± 1.39 | 9.64 ± 1.51 |
| **6e** | $CH_3(CH_2)_{11}$ | 15.99 ± 2.05 | 21.39 ± 2.39 | 2.21 ± 0.19 |
| **6f** | $CH_3(CH_2)_{13}$ | 7.83 ± 1.23 | 8.21 ± 1.29 | 1.85 ± 0.29 |
| **6g** | $CH_3(CH_2)_{15}$ | 19.99 ± 2.15 | 27.88 ± 2.48 | 3.30 ± 0.37 |
| **6h** | $CH_3(CH_2)_{17}$ | 17.80 ± 1.97 | 15.40 ± 1.83 | 7.58 ± 1.17 |
| **14a** | $CH_3(CH_2)_6$ | >128 | >128 | >128 |
| **14b** | $CH_3(CH_2)_7$ | >128 | >128 | >128 |
| **14c** | $CH_3(CH_2)_8$ | >128 | >128 | >128 |
| **14d** | $CH_3(CH_2)_9$ | 43.10 ± 3.34 | 57.39 ± 3.69 | 44.99 ± 2.89 |
| **14e** | $CH_3(CH_2)_{11}$ | 93.75 ± 3.90 | 115.08 ± 1.60 | 2.62 ± 0.06 |
| **14f** | $CH_3(CH_2)_{13}$ | 6.68 ± 1.06 | 8.79 ± 1.36 | 2.45 ± 0.05 |
| **14g** | $CH_3(CH_2)_{15}$ | 6.31 ± 1.01 | 5.34 ± 0.84 | 2.26 ± 0.01 |
| **14h** | $CH_3(CH_2)_{17}$ | 2.29 ± 0.06 | 3.11 ± 0.35 | 1.93 ± 0.09 |
| 5-Fu | | 9.45 ± 1.26 | 11.34 ± 1.14 | 3.52 ± 0.61 |
| Jaspine B | | 6.12 ± 0.79 | 5.10 ± 0.02 | 4.84 ± 0.68 |

[a] Inhibitory activity was assayed by exposure for 48 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.

reduced pressure. The residue was extracted with EtOAc (50 mL), and the organic layer was washed with brine (3 × 15 mL), dried over $MgSO_4$, and concentrated in vacuo to give pure **2** (176 mg, 95% yield) as colorless oil; $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 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, $CDCl_3$, ppm): $\delta$ 136.98, 128.71, 128.33, 127.94, 79.95, 79.56, 73.86, 69.38, 61.83, 61.22. HRMS (ESI): *m/z* calcd for $C_{12}H_{15}N_3O_3Na$ $[M+Na]^+$: 272.1108, found: 272.1110.

### 4.3. Procedure for the synthesis of (2S,3S,4S)-4-azido-3-(benzyloxy)-2-((prop-2-yn-1-yloxy)- methyl) tetrahydrofuran compound **3**

To a stirred solution of compound **2** (3.92 g, 15 mmol) and NaOH (2.75 g, 22.5 mmol) in $CH_3CN$ (60 mL) was added propargyl bromide dropwise (1.93 mL, 30 mmol) at 80 °C. After 4 h of stirring at this temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure to give an dark red oily residue, which was purified by column chromatography using the PE/EtOAc (10:1) as the eluent to afford compound **3** (3.76 g, 83% yield) as pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.44–7.34 (m, 5H), 4.82 (d, $J$ = 11.6 Hz, 1H), 4.65 (d, $J$ = 11.6 Hz, 1H), 4.27–4.22 (m, 2H), 4.17 (ddd, $J$ = 9.9, 6.3, 2.2 Hz, 2H), 3.97 (dd, $J$ = 5.8, 1.7 Hz, 2H), 3.95–3.89 (m, 1H), 3.82 (dd, $J$ = 10.1, 4.6 Hz, 1H), 3.73 (dd, $J$ = 10.1, 7.3 Hz, 1H), 2.45 (t, $J$ = 2.4 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 137.36, 128.52, 128.06, 127.93, 79.52, 79.46, 79.11, 74.69, 73.91, 69.03, 68.64, 61.22, 58.63.

### 4.4. Procedure for the synthesis of tert-butyl ((3S,4S,5S)-4-(benzyloxy)-5-((prop-2-yn-1-yloxy)-methyl)tetrahydrofuran-3-yl) carbamate compound **4**

To a stirred solution of **3** (2.76 g, 9.61 mmol) in THF/$H_2O$ (60 mL/10 mL) was added $PPh_3$ (7.14 g, 27.24 mmol). After 12 h of stirring at 65 °C the solvent was removed and a solution of di-tertbutyl dicarbonate (2.51 g, 11.50 mmol) in THF (40 mL) was added. The resulting solution was stirred at room temperature for 2 h and concentrated under reduced pressure. The residue was purified by column chromatography using the PE/EtOAc (10:1) as the eluent to obtain **4** as white solid (2.984 g, two-step yield 86%); Mp: 60–61 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.39–7.30 (m, 5H), 5.38 (d, $J$ = 8.8 Hz, 1H), 4.78 (d, $J$ = 11.9 Hz, 1H), 4.58 (d, $J$ = 11.9 Hz, 1H), 4.28–4.14 (m, 3H), 3.99 (dd, $J$ = 9.2, 3.7 Hz, 2H), 3.90–3.84 (m, 2H), 3.69 (dq, $J$ = 10.4, 3.0 Hz, 2H), 2.43 (s, 1H), 1.47 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): $\delta$ 155.37, 137.72, 128.45, 127.86, 127.79, 85.57, 83.85, 79.45, 78.93, 75.09, 73.08, 71.70, 69.67, 58.73, 55.69, 28.42. HRMS (ESI): *m/z* calcd for $C_{20}H_{27}NO_5Na$ $[M+Na]^+$: 384.1787, found: 384.1785.

### 4.5. General procedure for the synthesis of compounds **5a–5h**

To a solution of compound **4** (181 mg, 0.50 mmol) in THF/$H_2O$ (4 mL/8 mL) were added $CuSO_4$ (29.95 mg, 0.01 mmol), sodium ascorbate (20.16 mg, 0.012 mmol). After stirring for 10 min at room temperature, a solution of azide derivatives (0.75 mmol) in THF (4 mL) was added dropwise to the reaction mixture, which was then stirred at room temperature for about 2 h. THF was removed under reduced pressure and the residue was extracted with ethyl

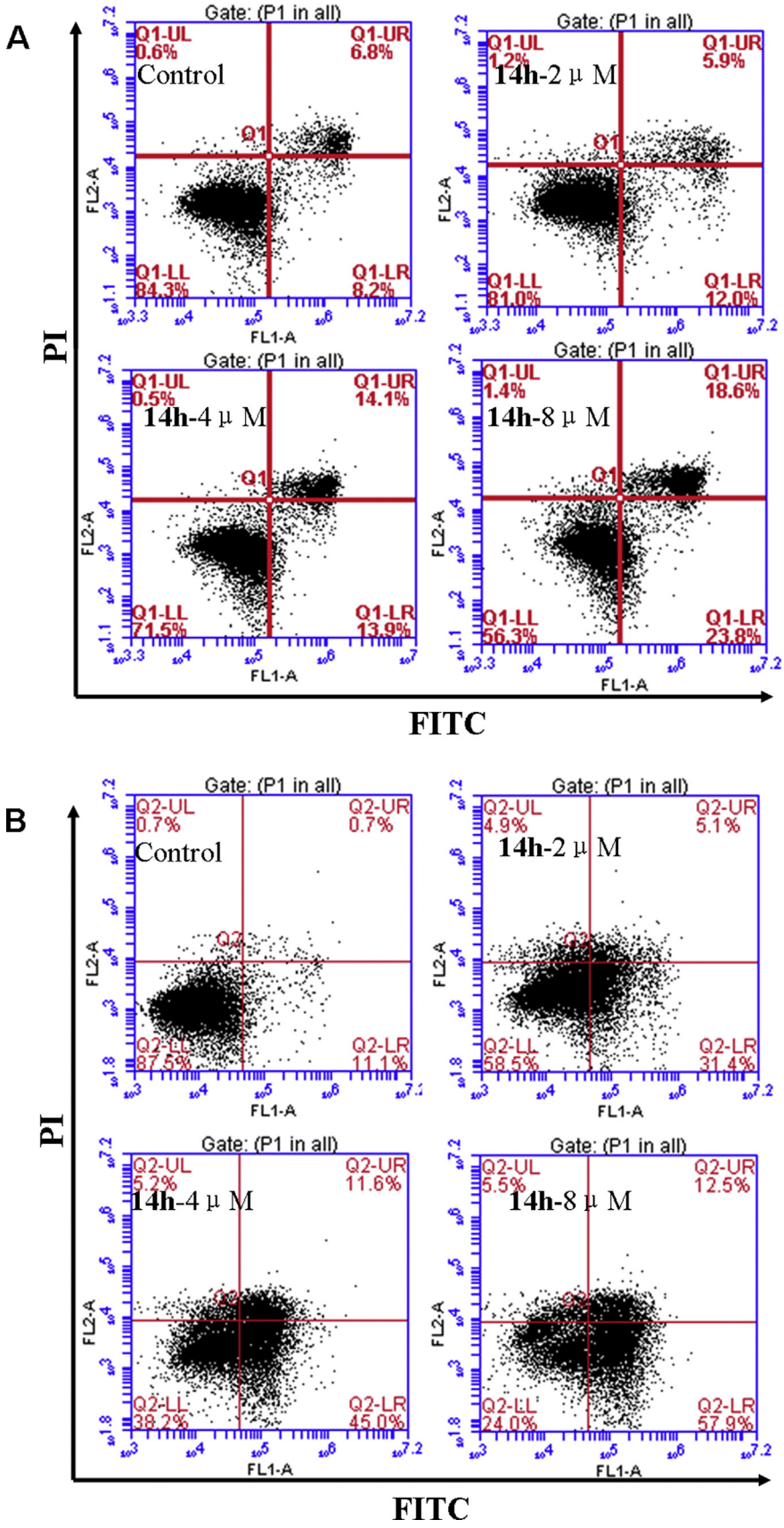



**Fig. 4.** Apoptosis effect on human MCF-7cell line induced by compound 14h. Apoptotic cells were detected with Annexin V/PI double staining after incubation with compounds 14h (0, 2, 4, 8 μM) for 8 h or 16 h. (A) incubated for 8 h; (B) incubated for 16 h. The lower left quadrants represent live cells, the lower right quadrants are for early/primary apoptotic cells, upper right quadrants are for late/secondary apoptotic cells, while the upper left quadrants represent cells damaged during the procedure. The experiments were performed three times, and a representative experiment is shown.

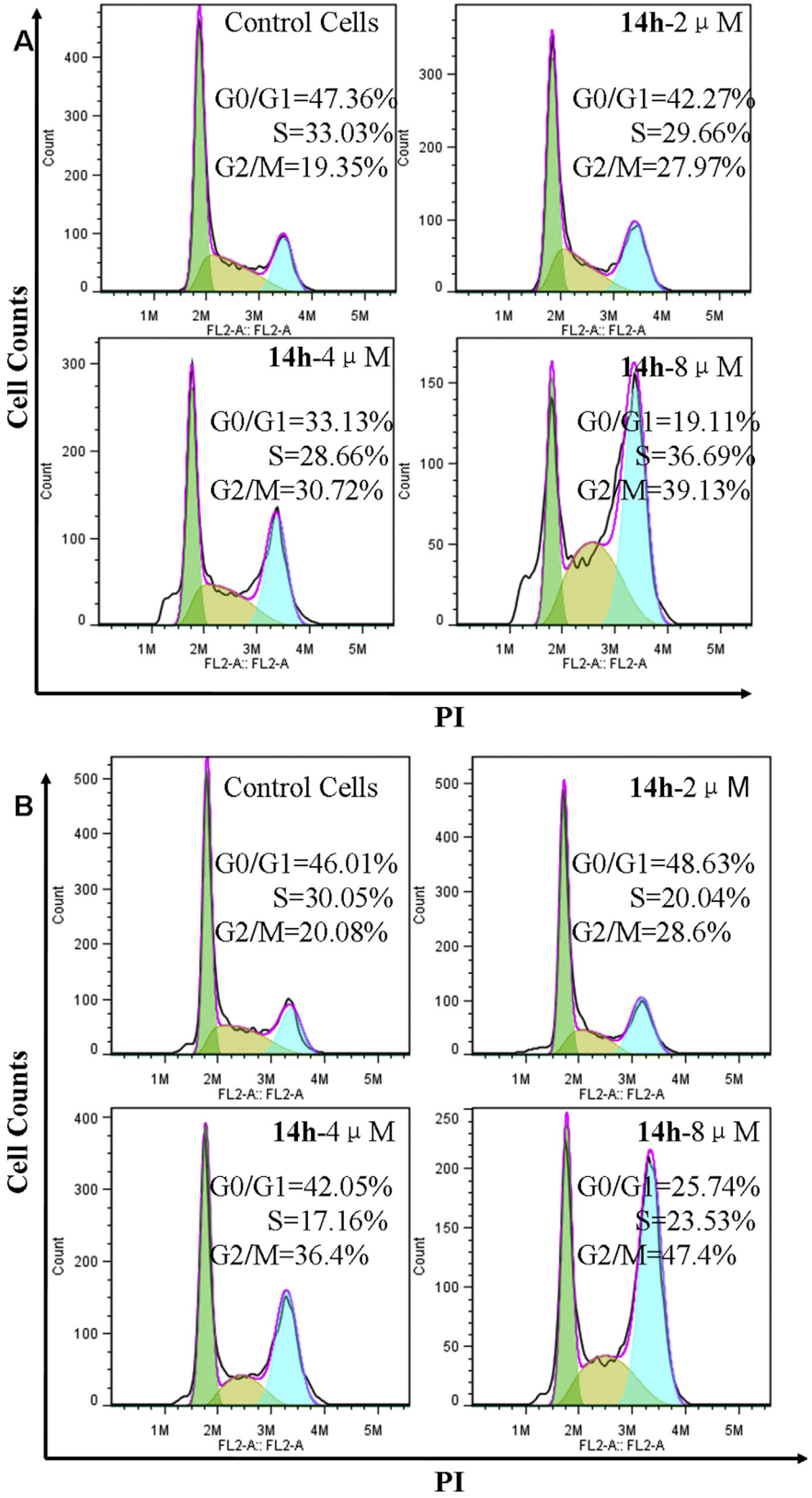



**Fig. 5.** Effect of compound **14h** on the cell cycle distribution of MCF-7 cells. Cells were treated with different concentrations (0, 2, 4, 8 μM) for 8 h or 16 h. Then the cells were fixed and stained with PI to analyze DNA content by flow cytometry. (A) incubated for 8 h; (B) incubated for 16 h. The experiments were performed three times, and a representative experiment is shown.

acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo followed by purification by column chromatography to yield the pure product.

*4.5.1. Tert-butyl ((3S,4S,5S)-4-(benzyloxy)-5-(((1-heptyl-1H-1, 2, 3-triazol-4-yl)methoxy)methyl) tetrahydrofuran-3-yl) carbamate (**5a**)*

Yield 79%. White solid. Mp: 48–49 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.49 (s, 1H), 7.45–7.31 (m, 5H), 5.40 (d, $J$ = 8.7 Hz, 1H), 4.72 (s, 2H), 4.57 (q, $J$ = 11.6 Hz, 2H), 4.42–4.34 (m, 1H), 4.27 (td, $J$ = 7.0, 1.5 Hz, 2H), 4.18–4.09 (m, 2H), 3.93 (dd, $J$ = 8.7, 6.6 Hz, 1H), 3.79–3.65 (m, 3H), 1.86 (p, $J$ = 7.2 Hz, 2H), 1.42 (d, $J$ = 13.0 Hz, 9H), 1.37–1.23 (m, 8H), 0.89 (t, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.69, 144.80, 137.62, 128.54, 128.00, 127.85, 122.26, 79.51, 79.25, 78.22, 73.72, 71.09, 68.86, 65.13, 52.03, 50.32, 31.55, 30.29, 28.65, 28.38, 26.44, 22.51, 14.02. HRMS (ESI): *m/z* calcd for $C_{27}H_{42}N_4O_5Na$ $(M+Na)^+$: 525.3053, found: 525.3054.

*4.5.2. Tert-butyl ((3S,4S,5S)-4-(benzyloxy)-5-(((1-octyl-1H-1,2,3-triazol-4-yl)methoxy)methyl) tetrahydrofuran-3-yl) carbamate (**5b**)*

Yield 83%. White solid. Mp: 53–54 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.49 (s, 1H), 7.43–7.31 (m, 5H), 5.40 (d, $J$ = 8.7 Hz, 1H), 4.72 (s, 2H), 4.58 (q, $J$ = 11.6 Hz, 2H), 4.42–4.35 (m, 1H), 4.31–4.23 (m, 2H), 4.14 (td, $J$ = 10.4, 5.5 Hz, 2H), 3.94 (dd, $J$ = 8.7, 6.7 Hz, 1H), 3.79–3.67 (m, 3H), 1.91–1.82 (m, 2H), 1.44 (s, 9H), 1.35–1.24 (m, 10H), 0.89 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.70, 144.82, 137.62, 128.55, 128.00, 127.86, 122.27, 79.53, 79.26, 78.23, 73.73, 71.09, 68.87, 65.12, 52.04, 50.33, 31.70, 30.30, 29.70, 29.04, 28.95, 28.39, 26.49, 22.59, 14.06. HRMS (ESI): *m/z* calcd for $C_{28}H_{44}N_4O_5Na$ $(M+Na)^+$: 539.3209, found: 539.3207.

*4.5.3. Tert-butyl ((3S,4S,5S)-4-(benzyloxy)-5-(((1-nonyl-1H-1,2,3-triazol-4-yl)methoxy)methyl) tetrahydrofuran-3-yl) carbamate (**5c**)*

Yield 85%. Pale pink solid. Mp: 49–50 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.49 (s, 1H), 7.43–7.30 (m, 5H), 5.40 (d, $J$ = 8.7 Hz, 1H), 4.72 (s, 2H), 4.66–4.49 (m, 2H), 4.44–4.34 (m, 1H), 4.28 (dt, $J$ = 7.6, 6.1 Hz, 2H), 4.20–4.08 (m, 2H), 3.93 (dd, $J$ = 8.8, 6.6 Hz, 1H), 3.81–3.64 (m, 3H), 1.91–1.79 (m, 2H), 1.45 (d, $J$ = 11.9 Hz, 9H), 1.36–1.20 (m, 12H), 0.89 (dd, $J$ = 9.0, 4.7 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.69, 144.85, 137.63, 128.54, 127.99, 127.85, 122.26, 79.50, 79.26, 78.23, 73.72, 71.10, 68.86, 65.14, 52.04, 50.32, 31.79, 30.30, 29.33, 29.16, 28.99, 28.38, 26.49, 22.63, 14.09. HRMS (ESI): *m/z* calcd for $C_{29}H_{46}N_4O_5$ Na $(M+Na)^+$: 553.3366, found: 553.3364.

*4.5.4. Tert-butyl ((3S,4S,5S)-4-(benzyloxy)-5-(((1-decyl-1H-1,2,3-triazol-4-yl)methoxy)methyl) tetrahydrofuran-3-yl) carbamate (**5d**)*

Yield 77%. White solid. Mp: 66–67 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.49 (s, 1H), 7.36 (dt, $J$ = 14.0, 5.0 Hz, 5H), 5.41 (d, $J$ = 8.8 Hz, 1H), 4.71 (s, 2H), 4.57 (q, $J$ = 11.6 Hz, 2H), 4.37 (dd, $J$ = 14.2, 7.1 Hz, 1H), 4.33–4.21 (m, 2H), 4.19–4.04 (m, 2H), 3.93 (dd, $J$ = 8.6, 6.7 Hz, 1H), 3.79–3.63 (m, 3H), 1.94–1.80 (m, 2H), 1.44 (d, $J$ = 6.1 Hz, 9H), 1.35–1.21 (m, 14H), 0.89 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.70, 137.62, 128.54, 127.99, 127.95, 127.85, 122.27, 79.51, 79.25, 78.22, 73.72, 71.08, 68.86, 65.12, 52.03, 50.33, 31.84, 30.29, 29.46, 29.37, 29.24, 28.99, 28.38, 26.49, 22.66, 14.10. HRMS (ESI): *m/z* calcd for $C_{30}H_{48}N_4O_5Na$ $(M+Na)^+$: 567.3522, found: 567.3524.

*4.5.5. Tert-butyl ((3S,4S,5S)-4-(benzyloxy)-5-(((1-dodecyl-1H-1,2,3-triazol-4-yl)methoxy)methyl) tetrahydrofuran-3-yl) carbamate (**5e**)*

Yield 82%. White solid. Mp: 63–64 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.44 (s, 1H), 7.40–7.31 (m, 5H), 5.36 (d, $J$ = 8.8 Hz, 1H), 4.72 (s, 2H), 4.57 (q, $J$ = 11.6 Hz, 2H), 4.43–4.34 (m, 1H), 4.27 (dd, $J$ = 7.6, 5.9 Hz, 2H), 4.19–4.10 (m, 2H), 3.98–3.88 (m, 1H), 3.78–3.68 (m, 3H), 1.90–1.81 (m, 2H), 1.45 (d, $J$ = 6.7 Hz, 9H), 1.29 (d, $J$ = 18.9 Hz, 22H), 0.89 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.69, 144.82, 137.62, 128.55, 128.00, 127.86, 122.24, 79.51, 79.26, 78.23, 73.72, 71.10, 68.87, 65.15, 52.04, 50.32, 31.90, 30.31, 29.60, 29.52, 29.39, 29.33, 29.01, 28.39, 26.51, 22.69, 14.12. HRMS (ESI): *m/z* calcd for $C_{32}H_{52}N_4O_5Na$ $(M+Na)^+$: 595.3835, found; 595.3835.

*4.5.6. Tert-butyl ((3S,4S,5S)-4-(benzyloxy)-5-(((1-tetradecyl-1H-1, 2, 3-triazol-4-yl)methoxy) methyl)tetrahydrofuran-3-yl) carbamate (**5f**)*

Yield 87%. White solid. Mp: 67–68 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.49 (s, 1H), 7.42–7.30 (m, 5H), 5.40 (d, $J$ = 8.8 Hz, 1H), 4.72 (s, 2H), 4.57 (q, $J$ = 11.6 Hz, 2H), 4.42–4.34 (m, 1H), 4.27 (dd, $J$ = 7.6, 5.9 Hz, 2H), 4.19–4.08 (m, 2H), 3.98–3.86 (m, 1H), 3.79–3.65 (m, 3H), 1.92–1.81 (m, 2H), 1.45 (d, $J$ = 6.7 Hz, 9H), 1.29 (d, $J$ = 18.9 Hz, 22H), 0.89 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.69, 144.81, 137.62, 128.54, 128.00, 127.85, 122.24, 79.50, 79.25, 78.22, 73.72, 71.16, 71.09, 68.86, 65.14, 52.03, 50.32, 31.92, 30.31, 29.67, 29.64, 29.60, 29.52, 29.39, 29.35, 29.01, 28.38, 26.50, 22.69, 14.13. HRMS (ESI): *m/z* calcd for $C_{34}H_{56}N_4O_5Na$ $(M+Na)^+$: 623.4148, found: 623.4147.

*4.5.7. Tert-butyl ((3S,4S,5S)-4-(benzyloxy)-5-(((1-hexadecyl-1H-1,2,3-triazol-4-yl)methoxy) methyl)tetrahydrofuran-3-yl) carbamate (**5g**)*

Yield 90%. White solid. Mp: 70–71 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.49 (s, 1H), 7.42–7.31 (m, 5H), 5.40 (d, $J$ = 8.7 Hz, 1H), 4.72 (s, 2H), 4.58 (q, $J$ = 11.6 Hz, 2H), 4.46–4.33 (m, 1H), 4.32–4.23 (m, 2H), 4.18–4.10 (m, 2H), 3.94 (dd, $J$ = 8.7, 6.7 Hz, 1H), 3.78–3.69 (m, 3H), 1.91–1.82 (m, 2H), 1.44 (s, 3H), 1.29 (d, $J$ = 19.0 Hz, 9H), 0.90 (t, $J$ = 6.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.69, 144.81, 137.62, 128.55, 128.00, 127.86, 122.24, 79.51, 79.25, 78.22, 73.72, 71.10, 68.86, 65.15, 52.03, 50.32, 31.93, 30.31, 29.69, 29.66, 29.61, 29.53, 29.39, 29.37, 29.01, 28.39, 26.51, 22.70, 14.13. HRMS (ESI): *m/z* calcd for $C_{36}H_{61}N_4O_5Na$ $(M+Na)^+$: 651.4456, found: 651.4464.

*4.5.8. Tert-butyl ((3S,4S,5S)-4-(benzyloxy)-5-(((1-octadecyl-1H-1,2,3-triazol-4-yl)methoxy) methyl) tetrahydrofuran-3-yl) carbamate (**5h**)*

Yield 89%. White solid. Mp: 81–82 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.49 (s, 1H), 7.44–7.31 (m, 5H), 5.40 (d, $J$ = 8.6 Hz, 1H), 4.72 (s, 2H), 4.58 (q, $J$ = 11.6 Hz, 2H), 4.44–4.34 (m, 1H), 4.27 (dd, $J$ = 7.6, 5.8 Hz, 2H), 4.18–4.11 (m, 2H), 3.94 (dd, $J$ = 8.7, 6.7 Hz, 1H), 3.78–3.66 (m, 3H), 1.91–1.82 (m, 2H), 1.44 (s, 9H), 1.29 (d, $J$ = 17.0 Hz, 30H), 0.90 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.69, 144.81, 137.62, 128.54, 128.00, 127.86, 122.24, 79.25, 78.23, 73.72, 71.10, 68.87, 65.15, 52.03, 50.32, 31.93, 30.31, 29.70, 29.66, 29.61, 29.54, 29.40, 29.37, 29.02, 28.39, 26.51, 22.70, 14.13. HRMS (IES): *m/z* calcd for $C_{38}H_{64}N_4O_5Na$ $(M + Na)^+$: 679.4774, found: 679.4778.

*4.6. General procedure for the synthesis of compounds **6a**–**6h***

A mixture of **5a**–**h** (0.31 mmol) and Pd/C (5% content, 30 mg) in methanol (50 mL) containing 0.1% HCl (v/v) was bubbled into hydrogen atmosphere at 60 °C and 60 atm pressure. The hydrogenation was kept at these conditions for about 3 h, the mixture was filtered through a short pad of silica gel and the silica pad was washed with MeOH/EtOAc (1:1), and the filtrate was concentrated. The residue was purified on a short silica gel column, which was pre-eluted with EtOAc containing 1% $NH_4OH$ (v/v) using EtOAc/methanol/$NH_4OH$ (70:10:1) as the eluent to furnish target compounds **6a**–**6h**.

*4.6.1. (2S,3S,4S)-4-Amino-2-(((1-heptyl-1H-1, 2, 3-triazol-4-yl) methoxy)methyl) tetrahydrofuran-3-ol (**6a**)*

Yield 71%. Colorless oil; $^1$H NMR (400 MHz, Acetone-$d_6$, ppm): $\delta$ 7.94 (s, 1H), 4.70–4.56 (m, 2H), 4.47 (dd, $J$ = 6.4, 3.5 Hz, 1H), 4.42 (t, $J$ = 7.1 Hz, 2H), 4.07–4.01 (m, 1H), 3.83–3.75 (m, 2H), 3.65–3.57 (m, 2H), 3.54 (dd, $J$ = 10.1, 5.0 Hz, 1H), 2.87 (s, 1H), 1.98–1.85 (m, 2H), 1.32 (ddd, $J$ = 9.2, 5.7, 2.7 Hz, 8H), 0.89 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, Acetone-$d_6$, ppm): $\delta$ 144.72, 122.88, 81.76, 81.11, 71.47, 68.90, 64.57, 64.37, 49.62, 31.51, 30.19, 28.42, 26.23, 22.33, 13.44. HRMS (ESI): *m/z* calcd for $C_{15}H_{29}N_4O_3$ $(M+H)^+$: 313.2235, found; 313.2235.

*4.6.2. (2S,3S,4S)-4-Amino-2-(((1-octyl-1H-1,2,3-triazol-4-yl) methoxy)methyl) tetrahydrofuran-3-ol (**6b**)*

Yield 75%. Yellow oil; $^1$H NMR (400 MHz, Acetone-$d_6$, ppm): $\delta$ 7.91 (s, 1H), 4.70–4.52 (m, 2H), 4.51–4.36 (m, 3H), 4.10–3.98 (m, 1H), 3.87–3.69 (m, 2H), 3.66–3.56 (m, 2H), 3.52 (dd, $J$ = 10.1, 5.0 Hz, 1H), 2.78 (s, 2H), 1.91 (dd, $J$ = 13.9, 7.0 Hz, 2H), 1.30 (dd, $J$ = 13.4, 5.4 Hz, 10H), 0.87 (t, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (100 MHz, Acetone-$d_6$, ppm): $\delta$ 144.73, 122.87, 81.77, 81.11, 71.46, 68.90, 64.55, 64.38, 49.62, 31.61, 30.19, 26.28, 22.39, 13.47. HRMS (ESI): *m/z* calcd for $C_{16}H_{31}N_4O_3$ $(M+H)^+$: 327.2391, found: 327.2394.

*4.6.3. (2S,3S,4S)-4-Amino-2-(((1-nonyl-1H-1, 2, 3-triazol-4-yl) methoxy)methyl) tetrahydrofuran-3-ol (**6c**)*

Yield 82%. Yellow solid. Mp: 51–52 °C; $^1$H NMR (400 MHz, Acetone-$d_6$, ppm): $\delta$ 7.93 (s, 1H), 4.71–4.56 (m, 2H), 4.48 (dd, $J$ = 6.4, 3.5 Hz, 1H), 4.42 (t, $J$ = 7.1 Hz, 2H), 4.12–3.98 (m, 1H), 3.79 (dt, $J$ = 7.1, 5.0 Hz, 2H), 3.64–3.57 (m, 2H), 3.55 (dd, $J$ = 10.1, 5.0 Hz, 1H), 1.99–1.85 (m, 2H), 1.34 (dd, $J$ = 15.0, 9.3 Hz, 12H), 0.90 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, Acetone-$d_6$, ppm): $\delta$ 144.72, 122.85, 81.77, 81.13, 71.43, 68.87, 64.51, 64.39, 49.62, 31.68, 30.19, 29.25, 29.06, 28.85, 26.27, 22.42, 13.48. HRMS (ESI): *m/z* calcd for $C_{17}H_{33}N_4O_3$ $(M + H)^+$: 341.2547, found: 341.2554.

*4.6.4. (2S,3S,4S)-4-Amino-2-(((1-decyl-1H-1,2,3-triazol-4-yl) methoxy)methyl) tetrahydrofuran-3-ol (**6d**)*

Yield 82%. White solid. Mp: 54–55 °C; $^1$H NMR (400 MHz, Acetone-$d_6$, ppm): $\delta$ 7.93 (s, 1H), 4.62 (q, $J$ = 12.2 Hz, 2H), 4.48 (dd, $J$ = 6.4, 3.5 Hz, 1H), 4.42 (t, $J$ = 7.1 Hz, 2H), 4.14–3.94 (m, 1H), 3.83–3.70 (m, 2H), 3.64–3.59 (m, 2H), 3.56–3.51 (m, 1H), 2.01–1.82 (m, 2H), 1.43–1.25 (m, 14H), 0.90 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, Acetone-$d_6$, ppm): $\delta$ 144.73, 122.85, 81.77, 81.12, 71.45, 68.89, 64.53, 64.39, 49.62, 31.73, 30.19, 29.30, 29.13, 28.85, 26.28, 22.44, 13.49. HRMS (ESI): *m/z* calcd for $C_{18}H_{35}N_4O_3$ $(M + H)^+$: 355.2704, found: 355.2702.

*4.6.5. (2S,3S,4S)-4-Amino-2-(((1-dodecyl-1H-1, 2, 3-triazol-4-yl) methoxy)methyl) tetrahydrofuran-3-ol (**6e**)*

Yield 84%. Yellow solid. Mp: 57–58 °C; $^1$H NMR (400 MHz, Acetone-$d_6$, ppm): $\delta$ 7.95 (s, 1H), 4.68–4.58 (m, 2H), 4.54 (dd, $J$ = 6.2, 3.3 Hz, 1H), 4.42 (t, $J$ = 7.1 Hz, 2H), 4.18–4.08 (m, 1H), 3.88 (d, $J$ = 10.3 Hz, 1H), 3.80 (dd, $J$ = 13.9, 7.2 Hz, 1H), 3.64 (t, $J$ = 7.6 Hz, 2H), 3.60–3.53 (m, 1H), 1.98–1.86 (m, 2H), 1.33 (d, $J$ = 18.4 Hz, 18H), 0.89 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, Acetone-$d_6$, ppm): $\delta$ 144.66, 122.93, 81.69, 81.25, 71.12, 68.71, 64.36, 64.20, 49.65, 31.76, 30.20, 29.48, 29.32, 28.88, 26.29, 22.46, 13.52. HRMS (ESI): *m/z* calcd for $C_{20}H_{39}N_4O_3$ $(M + H)^+$: 383.3017, found: 383.3019.

*4.6.6. (2S,3S,4S)-4-Amino-2-(((1-tetradecyl-1H-1,2,3-triazol-4-yl) methoxy)methyl) tetrahydrofuran-3-ol (**6f**)*

Yield 82%. White solid. Mp: 63–64 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.57 (s, 1H), 4.70 (q, $J$ = 12.4 Hz, 2H), 4.33 (t, $J$ = 7.3 Hz, 2H), 4.04 (dd, $J$ = 9.1, 5.7 Hz, 1H), 3.94–3.89 (m, 1H), 3.86 (dd, $J$ = 8.6, 4.7 Hz, 1H), 3.73 (qd, $J$ = 10.4, 4.1 Hz, 2H), 3.63 (dd, $J$ = 9.1, 4.3 Hz, 1H), 3.35 (dd, $J$ = 9.6, 4.2 Hz, 1H), 2.75 (s, 3H), 1.96–1.83 (m, 2H), 1.39–1.18 (m, 22H), 0.89 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): $\delta$ 144.59, 122.47, 84.10, 79.66, 74.04, 70.73, 64.72, 59.71, 50.44, 31.91, 30.27, 29.67, 29.63, 29.60, 29.52, 29.39, 29.34, 29.00, 26.51, 22.68, 14.11. HRMS (ESI): *m/z* calcd for $C_{22}H_{43}N_4O_3$ $(M+H)^+$: 411.3330, found: 411.3337.

*4.6.7. (2S,3S,4S)-4-amino-2-(((1-hexadecyl-1H-1,2,3-triazol-4-yl) methoxy)methyl) tetrahydrofuran-3-ol (**6g**)*

Yield 79%. Yellow solid. Mp: 70–71 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.54 (s, 1H), 4.71 (q, $J$ = 12.5 Hz, 2H), 4.33 (t, $J$ = 7.3 Hz, 2H), 4.15–4.14 (m, 1H), 4.06 (dd, $J$ = 9.7, 4.8 Hz, 1H), 3.98–3.90 (m, 1H), 3.85 (dd, $J$ = 10.2, 4.6 Hz, 1H), 3.77 (dd, $J$ = 10.2, 5.5 Hz, 1H), 3.64–3.59 (m, 2H), 2.67 (s, 3H), 1.96–1.82 (m, 2H), 1.28 (d, $J$ = 25.4 Hz, 26H), 0.88 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): $\delta$ 144.65, 122.13, 80.53, 72.25, 71.71, 69.50, 64.84, 54.21, 50.39, 31.89, 30.24, 29.65, 29.62, 29.57, 29.49, 29.35, 29.32, 28.97, 26.46, 22.66, 14.09. HRMS (ESI): *m/z* calcd for C24H47N4O3 $(M+H)^+$: 439.3643, found: 439.3647.

*4.6.8. (2S,3S,4S)-4-amino-2-(((1-octadecyl-1H-1,2,3-triazol-4-yl) methoxy)methyl) tetrahydrofuran-3-ol (**6h**)*

Yield 86%. White solid. Mp: 61–62 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.57 (s, 1H), 4.80–4.65 (m, 2H), 4.33 (t, $J$ = 7.3 Hz, 2H), 4.06 (dd, $J$ = 6.2, 4.6 Hz, 1H), 3.90 (d, $J$ = 10.6 Hz, 1H), 3.89–3.82 (m, 1H), 3.76–3.68 (m, 2H), 3.61 (dd, $J$ = 10.6, 4.6 Hz, 1H), 1.96–1.85 (m, 2H), 1.34–1.20 (m, 30H), 0.89 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): $\delta$ 145.00, 122.29, 81.68, 80.79, 71.54, 69.40, 65.05, 64.78, 50.34, 31.93, 30.31, 29.70, 29.66, 29.61, 29.53, 29.39, 29.37, 29.02, 26.52, 22.70, 14.13. HRMS (ESI): *m/z* calcd for $C_{26}H_{51}N_4O_3$ $(M+H)^+$: 467.3956, found: 467.3962.

*4.7. Procedure for the synthesis of (2R,3R,4S)-4-azido-3-(benzyloxy)-2-(dimethoxymethyl)-tetrahydrofuran compound **8***

To a solution of compound **7** (6.00 g, 30 mmol) in THF (100 mL) were added NaOH (1.60 g, 40 mmol) and benzyl bromide (6.00 g, 35 mmol). The solution was heated under reflux for 6 h. The mixture was filtered and the solid was washed with EtOAc. The combined filtrates were evaporated and the residue was partitioned between EtOAc and brine, the organic layer was dried over $Na_2SO_4$, and concentrated under vacuum. The residue was purified by column chromatography eluted with PE/EtOAc (15:1) to afford **8** (7.82 g, 90.3%) as colorless oil; $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 3.45 (s, 3H), 3.47 (s, 3H), 3.95–4.07 (m, 5H), 4.37 (d, $J$ = 6.3 Hz), 4.63 (q, $J$ = 11.8 Hz, 2H), 7.30–7.42 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): $\delta$ 54.1, 55.5,65.7, 70.9, 72.1, 84.2, 84.5, 103.8,128.0, 128.0, 128.5, 137.3. HRMS (ESI): *m/z* calcd for $C_{14}H_{19}N_3O_4Na$ $[M+Na]^+$: 316.1273, found: 316.1273.

*4.8. Procedure for the synthesis of (2R,3R,4S)-4-azido-3-(benzyloxy) tetrahydrofuran-2-carbaldehyde compound **9***

TFA (2.28 g, 20 mmol) was added to a solution of compound **8** (3.00 g, 10 mmol) in $CH_2Cl_2$ (40 mL) at 0 °C. The reaction mixture was warmed to 40 °C and stirred for 3 h. Upon completion, the mixture was washed with brine and the organic layer was concentrated under reduced pressure to obtain compound **9** (2.30 g, 91%) as colorless oil, which was used directly without further purification.

*4.9. Procedure for the synthesis of ((2S,3R,4S)-4-azido-3-(benzyloxy)tetrahydrofuran-2-yl)-methanol compound **10***

The procedure for the synthesis of compound **2** was the same as compound **10**. 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.

*4.10. Procedure for the synthesis of (2S,3R,4S)-4-azido-3-(benzyloxy)-2-((prop-2-yn-1-yloxy)-methyl) tetrahydrofuran compound **11***

The procedure for the synthesis of compound **3** was the same as compound **11**. Yield 85%. Yellow oil; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.44–7.30 (m, 5H), 4.68–4.58 (m, 2H), 4.23 (d, $J$ = 2.4 Hz, 2H), 4.03 (ddd, $J$ = 17.9, 7.8, 3.8 Hz, 4H), 3.96 (d, $J$ = 4.5 Hz, 1H), 3.69 (d, $J$ = 5.2 Hz, 2H), 2.47 (dd, $J$ = 2.8, 1.7 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 137.23, 128.58, 128.10, 127.89, 84.80, 83.05, 79.34, 74.89, 72.34, 70.95, 69.39, 65.76, 58.66.

*4.11. Procedure for the synthesis of tert-butyl ((3S,4R,5S)-4-(benzyloxy)-5-((prop-2-yn-1-yloxy) methyl)tetrahydrofuran-3-yl) carbamate compound **12***

The procedure for the synthesis of compound **4** was the same as compound **12**. Yield 88%. Yellow solid. Mp: 54–55 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.39–7.30 (m, 5H), 5.38 (d, $J$ = 8.8 Hz, 1H), 4.78 (d, $J$ = 11.9 Hz, 1H), 4.58 (d, $J$ = 11.9 Hz, 1H), 4.28–4.14 (m, 3H), 3.99 (dd, $J$ = 9.2, 3.7 Hz, 2H), 3.90–3.84 (m, 2H), 3.69 (qd, $J$ = 10.4, 3.0 Hz, 2H), 2.43 (s, 1H), 1.47 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.37, 137.75, 128.43, 127.84, 127.77, 85.60, 83.84, 78.95, 77.67, 75.05, 73.04, 71.70, 69.69, 67.91, 58.72, 28.40. HRMS (ESI): *m/z* calcd for $C_{20}H_{27}NO_5Na$ $[M+Na]^+$: 384.1787, found: 384.1789.

*4.12. General procedure for the synthesis of compounds **13a**–**13h***

The procedure for the synthesis of compounds **5a**–**h** was the same as compounds **13a**–**h**.

*4.12.1. Tert-butyl ((3S,4R,5S)-4-(benzyloxy)-5-(((1-heptyl-1H-1,2,3-triazol-4-yl)methoxy)methyl) tetrahydrofuran-3-yl) carbamate (**13a**)*

Yield 88%. Pale pink solid. Mp: 50–51 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.52 (s, 1H), 7.34 (s, 5H), 5.43 (d, $J$ = 8.6 Hz, 1H), 4.72 (dt, $J$ = 17.4, 9.1 Hz, 3H), 4.55 (d, $J$ = 11.8 Hz, 1H), 4.34 (t, $J$ = 7.3 Hz, 2H), 4.26–4.18 (m, 1H), 4.05–3.94 (m, 2H), 3.90–3.77 (m, 2H), 3.74 (d, $J$ = 10.6 Hz, 1H), 3.64 (dd, $J$ = 10.5, 3.6 Hz, 1H), 1.98–1.82 (m, 2H), 1.45 (s, 9H), 1.31 (ddd, $J$ = 9.6, 6.4, 4.0 Hz, 8H), 0.89 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.29, 144.45, 137.70, 128.42, 127.81, 122.22, 85.71, 83.97, 79.43, 73.03, 71.71, 70.56, 65.09, 55.81, 50.40, 31.55, 30.33, 28.65, 28.42, 26.46, 22.51, 14.01. HRMS (ESI): *m/z* calcd for $C_{27}H_{42}N_4O_5Na$ $(M+Na)^+$: 525.3053, found: 525.3054.

*4.12.2. Tert-butyl ((3S,4R,5S)-4-(benzyloxy)-5-(((1-octyl-1H-1,2,3-triazol-4-yl) methoxy) methyl) tetrahydrofuran-3-yl) carbamate (**13b**)*

Yield 84%. Pale pink solid. Mp: 60–61 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.52 (s, 1H), 7.34 (s, 5H), 5.43 (d, $J$ = 8.6 Hz, 1H), 4.72 (dt, $J$ = 17.4, 9.3 Hz, 3H), 4.55 (d, $J$ = 11.8 Hz, 1H), 4.34 (t, $J$ = 7.3 Hz, 2H), 4.22 (dd, $J$ = 8.3, 3.4 Hz, 1H), 4.01–3.92 (m, 2H), 3.89–3.77 (m, 2H), 3.74 (d, $J$ = 10.6 Hz, 1H), 3.64 (dd, $J$ = 10.5, 3.7 Hz, 1H), 1.92 (d, $J$ = 6.6 Hz, 2H), 1.48 (d, $J$ = 18.3 Hz, 9H), 1.30 (dd, $J$ = 16.7, 8.6 Hz, 10H), 0.89 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.29, 144.44, 137.70, 128.43, 127.82, 122.24, 85.70, 83.98, 79.43, 73.04, 71.71, 70.56, 65.09, 55.79, 50.41, 31.70, 30.34, 29.04, 28.96, 28.43, 26.51, 22.60, 14.07. HRMS (ESI): *m/z* calcd for $C_{28}H_{44}N_4O_5Na$ $(M+Na)^+$: 539.3209, found: 539.3207.

*4.12.3. Tert-butyl ((3S,4R,5S)-4-(benzyloxy)-5-(((1-nonyl-1H-1, 2, 3-triazol-4-yl)methoxy)methyl) tetrahydrofuran-3-yl) carbamate (**13c**)*

Yield 81%. White solid. Mp: 65–66 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.50 (s, 1H), 7.33 (d, $J$ = 5.2 Hz, 5H), 5.42 (d, $J$ = 8.7 Hz, 1H), 4.71 (dt, $J$ = 17.4, 9.5 Hz, 3H), 4.54 (d, $J$ = 11.8 Hz, 1H), 4.32 (t, $J$ = 7.3 Hz, 2H), 4.20 (dd, $J$ = 8.6, 3.5 Hz, 1H), 4.03–3.92 (m, 2H), 3.90–3.76 (m, 2H), 3.76–3.68 (m, 1H), 3.62 (dd, $J$ = 10.6, 3.8 Hz, 1H), 1.90 (d, $J$ = 6.7 Hz, 2H), 1.46 (d, $J$ = 18.6 Hz, 9H), 1.27 (dd, $J$ = 26.9, 11.7 Hz, 12H), 0.88 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.29, 144.43, 137.69, 128.43, 127.82, 122.24, 85.69, 83.98, 79.44, 73.05, 71.71, 70.55, 65.09, 55.78, 50.41, 31.80, 30.35, 29.71, 29.34, 29.18, 29.01, 28.43, 26.51, 22.64, 14.11. HRMS (ESI): *m/z* calcd for $C_{29}H_{47}N_4O_5$ $(M + H)^+$: 531.3541, found: 531.3547.

*4.12.4. Tert-butyl ((3S,4R,5S)-4-(benzyloxy)-5-(((1-decyl-1H-1, 2, 3-triazol-4-yl)methoxy)methyl)tetrahydrofuran-3-yl) carbamate (**13d**)*

Yield 85%. White solid. Mp: 73–74 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.51 (d, $J$ = 6.8 Hz, 1H), 7.33 (d, $J$ = 7.1 Hz, 5H), 5.42 (s, 1H), 4.73 (dt, $J$ = 11.7, 6.7 Hz, 3H), 4.55 (dd, $J$ = 11.7, 7.3 Hz, 1H), 4.33 (q, $J$ = 7.3 Hz, 2H), 4.21 (s, 1H), 3.98 (s, 2H), 3.84 (dd, $J$ = 16.3, 8.4 Hz, 2H), 3.75 (d, $J$ = 8.2 Hz, 1H), 3.69–3.55 (m, 1H), 1.90 (d, $J$ = 6.0 Hz, 2H), 1.45 (d, $J$ = 6.9 Hz, 9H), 1.28 (t, $J$ = 12.9 Hz, 14H), 0.89 (q, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.28, 144.43, 137.69, 128.42, 127.81, 122.22, 85.70, 83.98, 79.43, 73.04, 71.71, 70.55, 65.09, 55.77, 50.41, 31.85, 30.34, 29.47, 29.39, 29.25, 29.01, 28.43, 26.52, 22.67, 14.12. HRMS (ESI): *m/z* calcd for $C_{30}H_{48}N_4O_5Na$ $(M+Na)^+$: 567.3522, found: 567.3521.

*4.12.5. Tert-butyl ((3S,4R,5S)-4-(benzyloxy)-5-(((1-dodecyl-1H-1, 2, 3-triazol-4-yl)methoxy)-methyl)tetrahydrofuran-3-yl) carbamate (**13e**)*

Yield 85%. White solid. Mp: 71–72 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.50 (s, 1H), 7.33 (d, $J$ = 5.4 Hz, 5H), 5.41 (d, $J$ = 8.6 Hz, 1H), 4.71 (dt, $J$ = 17.3, 9.4 Hz, 3H), 4.54 (d, $J$ = 11.8 Hz, 1H), 4.33 (dd, $J$ = 14.0, 7.1 Hz, 2H), 4.19 (dd, $J$ = 10.7, 7.1 Hz, 1H), 4.00–3.92 (m, 2H), 3.87–3.76 (m, 2H), 3.73 (d, $J$ = 10.5 Hz, 1H), 3.62 (dd, $J$ = 10.6, 3.8 Hz, 1H), 1.90 (d, $J$ = 6.6 Hz, 2H), 1.44 (s, 9H), 1.35–1.18 (m, 18H), 0.93–0.82 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.29, 144.43, 137.69, 128.43, 127.82, 122.23, 85.69, 83.98, 79.44, 73.05, 71.71, 70.55, 65.09, 55.78, 50.42, 31.91, 30.36, 29.71, 29.60, 29.53, 29.40, 29.34, 29.02, 28.43, 26.52, 22.69, 14.13.

HRMS (ESI): *m/z* calcd for $C_{32}H_{52}N_4O_5Na$ $(M+Na)^+$: 595.3835, found: 595.3838.

*4.12.6. Tert-butyl ((3S,4R,5S)-4-(benzyloxy)-5-(((1-tetradecyl-1H-1, 2, 3-triazol-4-yl)methoxy)-methyl)tetrahydrofuran-3-yl) carbamate (**13f**)*

Yield 81%. White solid. Mp: 58–59 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.51 (s, 1H), 7.34 (s, 5H), 5.43 (d, $J$ = 8.6 Hz, 1H), 4.73 (dd, $J$ = 15.4, 8.5 Hz, 2H), 4.55 (d, $J$ = 11.8 Hz, 1H), 4.33 (t, $J$ = 7.3 Hz, 2H), 4.22 (d, $J$ = 5.1 Hz, 1H), 3.98 (s, 2H), 3.89–3.79 (m, 2H), 3.74 (d, $J$ = 10.2 Hz, 1H), 3.70–3.59 (m, 1H), 1.90 (s, 2H), 1.45 (s, 9H), 1.30 (d, $J$ = 26.2 Hz, 22H), 0.89 (t, $J$ = 6.6 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.29, 144.44, 137.70, 128.41, 127.81, 122.22, 85.70, 83.97, 79.42, 73.01, 71.70, 70.55, 65.07, 55.81, 50.40, 31.91, 30.33, 29.67, 29.63, 29.59, 29.52, 29.38, 29.34, 29.00, 28.42, 26.51, 22.68, 14.12. HRMS (ESI): *m/z* calcd for $C_{34}H_{56}N_4O_5Na$ $(M+Na)^+$: 623.4148, found: 623.4148.

*4.12.7. Tert-butyl ((3S,4R,5S)-4-(benzyloxy)-5-(((1-hexadecyl-1H-1, 2, 3-triazol-4-yl)methoxy)-methyl)tetrahydrofuran-3-yl) carbamate (**13g**)*

Yield 84%. White solid. Mp: 61–62 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.50 (s, 1H), 7.33 (d, *J* = 5.4 Hz, 5H), 5.41 (d, *J* = 8.5 Hz, 1H), 4.71 (dt, *J* = 17.4, 9.4 Hz, 3H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.32 (t, *J* = 7.3 Hz, 2H), 4.25–4.16 (m, 1H), 4.01–3.90 (m, 2H), 3.89–3.77 (m, 2H), 3.72 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.62 (dd, *J* = 10.6, 3.7 Hz, 1H), 1.90 (d, *J* = 6.6 Hz, 2H), 1.44 (s, 9H), 1.28 (d, *J* = 26.8 Hz, 26H), 0.88 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.29, 144.44, 137.70, 128.42, 127.81, 122.21, 85.70, 83.98, 79.43, 73.04, 71.71, 70.56, 65.10, 55.80, 50.41, 31.93, 30.35, 29.69, 29.66, 29.61, 29.53, 29.40, 29.37, 29.02, 28.43, 26.53, 22.70, 14.13. HRMS (ESI): *m/z* calcd for $C_{36}H_{60}N_4O_5Na$ $(M+Na)^+$: 651.4461, found: 651.4463.

*4.12.8. Tert-butyl ((3S,4R,5S)-4-(benzyloxy)-5-(((1-octadecyl-1H-1,2,3-triazol-4-yl)methoxy)-methyl)tetrahydrofuran-3-yl) carbamate (**13h**)*

Yield 90%. White solid. Mp: 74–75 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.52 (s, 1H), 7.34 (s, 5H), 5.44 (d, *J* = 8.5 Hz, 1H), 4.81–4.64 (m, 3H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.34 (t, *J* = 7.3 Hz, 2H), 4.22 (d, *J* = 5.0 Hz, 1H), 3.99 (s, 2H), 3.91–3.77 (m, 2H), 3.74 (d, *J* = 10.5 Hz, 1H), 3.68–3.59 (m, 1H), 1.92 (d, *J* = 6.4 Hz, 2H), 1.45 (s, 9H), 1.37–1.22 (m, 30H), 0.90 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 155.30, 144.43, 137.70, 128.42, 127.81, 122.25, 85.70, 83.97, 79.44, 73.00, 71.71, 70.56, 65.05, 55.83, 50.42, 31.92, 30.33, 29.69, 29.65, 29.60, 29.53, 29.39, 29.36, 29.01, 28.42, 27.41, 26.52, 22.69, 14.12. HRMS (ESI): *m/z* calcd for $C_{38}H_{64}N_4O_5Na$ $(M+Na)^+$: 679.4778, found: 679.4778.

*4.13. General procedure for the synthesis of compounds **14a**–**14h***

The procedure for the synthesis of compounds **6a**–**h** was the same as compounds **14a**–**h**.

*4.13.1. (2S,3R,4S)-4-Amino-2-(((1-heptyl-1H-1,2,3-triazol-4-yl) methoxy)methyl) tetrahydrofuran-3-ol (**14a**)*

Yield 79%. Yellow oil; $^1$H NMR (400 MHz, Acetone-$d_6$, ppm): δ 7.96 (d, *J* = 9.8 Hz, 1H), 4.63 (s, 2H), 4.42 (t, *J* = 7.2 Hz, 2H), 4.01 (ddd, *J* = 11.7, 9.8, 6.6 Hz, 2H), 3.88 (ddd, *J* = 7.7, 5.7, 3.9 Hz, 1H), 3.73–3.68 (m, 1H), 3.66 (dd, *J* = 7.2, 2.7 Hz, 1H), 3.64–3.59 (m, 1H), 1.98–1.88 (m, 2H), 1.39–1.24 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, Acetone-$d_6$, ppm): δ 144.72, 122.96, 84.06, 78.89, 71.66, 70.87, 67.70, 64.42, 49.66, 31.50, 30.17, 28.42, 26.24, 22.33, 13.44. HRMS (ESI): *m/z* calcd for $C_{15}H_{29}N_4O_3$ $(M+H)^+$: 313.2235, found: 313.2235.

*4.13.2. (2S,3R,4S)-4-amino-2-(((1-octyl-1H-1,2,3-triazol-4-yl) methoxy)methyl) tetrahydrofuran-3-ol (**14b**)*

Yield 84%. Yellow oil; $^1$H NMR (400 MHz, Acetone-$d_6$, ppm): δ 7.94 (s, 1H), 4.63 (s, 2H), 4.42 (t, *J* = 7.2 Hz, 2H), 4.06–3.95 (m, 3H), 3.89 (dd, *J* = 5.9, 4.2 Hz, 1H), 3.70 (dd, *J* = 10.5, 4.2 Hz, 1H), 3.67–3.59 (m, 2H), 1.99–1.86 (m, 5H), 1.56–1.17 (m, 10H), 0.89 (t, *J* = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, Acetone-$d_6$, ppm): δ 144.73, 122.93, 84.07, 78.95, 71.69, 70.87, 67.73, 64.42, 49.65, 31.60, 30.16, 26.27, 22.38, 21.53, 13.45. HRMS (ESI): *m/z* calcd for $C_{16}H_{31}N_4O_3$ $(M+H)^+$: 327.2391, found: 327.2394.

*4.13.3. (2S,3R,4S)-4-amino-2-(((1-nonyl-1H-1,2,3-triazol-4-yl) methoxy)methyl) tetrahydrofuran-3-ol (**14c**)*

Yield 81%. Colorless oil; $^1$H NMR (400 MHz, Acetone-$d_6$, ppm): δ 7.94 (s, 1H), 4.63 (s, 2H), 4.42 (t, *J* = 7.2 Hz, 2H), 4.05–3.97 (m, 2H), 3.89 (dt, *J* = 10.0, 5.1 Hz, 1H), 3.73–3.68 (m, 1H), 3.67–3.60 (m, 2H), 1.93 (dd, *J* = 14.1, 7.1 Hz, 2H), 1.42–1.25 (m, 12H), 0.90 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, Acetone-$d_6$, ppm): δ 144.72, 122.93, 84.09, 78.94, 71.69, 70.86, 67.72, 64.42, 49.65, 31.68, 30.17, 29.25, 29.06, 28.85, 26.27, 22.41, 13.47. HRMS (ESI): *m/z* calcd for $C_{17}H_{33}N_4O_3$ $(M+H)^+$: 341.2547, found: 341.2552.

*4.13.4. (2S,3R,4S)-4-amino-2-(((1-decyl-1H-1, 2, 3-triazol-4-yl) methoxy)methyl) tetrahydrofuran-3-ol (**14d**)*

Yield 85%. Pale yellow oil; $^1$H NMR (400 MHz, Acetone-$d_6$, ppm): δ 7.94 (s, 1H), 4.63 (s, 2H), 4.42 (t, *J* = 7.2 Hz, 2H), 4.01 (dd, *J* = 8.2, 3.7 Hz, 2H), 3.89 (dt, *J* = 10.0, 5.1 Hz, 1H), 3.70 (dd, *J* = 10.5, 4.1 Hz, 1H), 3.63 (dt, *J* = 13.8, 5.1 Hz, 2H), 1.96–1.89 (m, 2H), 1.88 (s, 3H), 1.41–1.26 (m, 14H), 0.90 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, Acetone-$d_6$, ppm): δ 144.73, 122.93, 84.07, 78.93, 71.68, 70.88, 67.74, 64.43, 49.66, 31.72, 29.30, 29.12, 28.85, 26.28, 22.43, 13.48. HRMS (ESI): *m/z* calcd for $C_{18}H_{35}N_4O_3$ $(M+H)^+$: 355.2704, found: 355.2707.

*4.13.5. (2S,3R,4S)-4-amino-2-(((1-dodecyl-1H-1,2,3-triazol-4-yl) methoxy)methyl) tetrahydrofuran-3-ol (**14e**)*

Yield 76%. Yellow oil; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.57 (s, 1H), 4.78–4.63 (m, 2H), 4.34 (t, *J* = 7.3 Hz, 2H), 4.05 (dd, *J* = 9.1, 5.7 Hz, 1H), 3.95–3.89 (m, 1H), 3.86 (dd, *J* = 8.7, 4.7 Hz, 1H), 3.79–3.68 (m, 2H), 3.64 (dd, *J* = 9.1, 4.4 Hz, 1H), 3.36 (dd, *J* = 9.6, 4.2 Hz, 1H), 2.59 (s, 3H), 1.97–1.83 (m, 2H), 1.38–1.18 (m, 18H), 0.89 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 144.60, 122.45, 84.06, 79.74, 74.04, 70.73, 64.72, 59.70, 50.44, 31.89, 30.27, 29.63, 29.59, 29.52, 29.38, 29.32, 29.00, 26.51, 22.67, 14.11. HRMS (ESI): *m/z* calcd for $C_{20}H_{39}N_4O_3$ $(M+H)^+$: 383.3017, found: 383.3021.

*4.13.6. (2S,3R,4S)-4-Amino-2-(((1-tetradecyl-1H-1, 2, 3-triazol-4-yl)methoxy)methyl) tetrahydrofuran-3-ol (**14f**)*

Yield 87%. White solid. Mp: 76–77 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.58 (s, 1H), 4.69 (q, *J* = 12.3 Hz, 2H), 4.33 (t, *J* = 7.3 Hz, 2H), 4.04 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.99–3.92 (m, 1H), 3.87 (dd, *J* = 8.4, 4.5 Hz, 1H), 3.73 (qd, *J* = 10.5, 4.0 Hz, 2H), 3.66 (dd, *J* = 9.2, 4.1 Hz, 1H), 3.37 (dd, *J* = 9.1, 3.8 Hz, 1H), 3.10 (s, 3H), 1.94–1.85 (m, 2H), 1.29 (d, *J* = 24.8 Hz, 22H), 0.89 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$. ppm): δ 144.48, 122.54, 84.16, 79.24, 73.72, 70.61, 64.66, 59.55, 50.45, 31.91, 30.26, 29.67, 29.63, 29.60, 29.52, 29.39, 29.34, 29.00, 26.51, 22.67, 14.11. HRMS (ESI): *m/z* calcd for $C_{22}H_{43}N_4O_3$ $(M+H)^+$: 411.3330, found: 411.3337.

*4.13.7. (2S,3R,4S)-4-Amino-2-(((1-hexadecyl-1H-1,2,3-triazol-4-yl) methoxy)methyl)tetrahydrofuran-3-ol (**14g**)*

Yield 88%. Yellow solid. Mp: 81–82 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.57 (s, 1H), 4.77–4.63 (m, 2H), 4.34 (t, *J* = 7.3 Hz, 2H), 4.05 (dd, *J* = 9.1, 5.7 Hz, 1H), 3.91 (dd, *J* = 11.1, 7.2 Hz, 1H), 3.86 (dd, *J* = 8.7, 4.7 Hz, 1H), 3.80–3.68 (m, 2H), 3.63 (dd, *J* = 9.1, 4.4 Hz, 1H), 3.35 (dd, *J* = 9.6, 4.2 Hz, 1H), 2.59 (s, 3H), 1.89 (dd, *J* = 13.6, 6.7 Hz, 2H), 1.36–1.20 (m, 24H), 0.89 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 144.60, 122.47, 84.10, 79.69, 74.08, 70.74, 64.72, 59.72, 50.44, 31.91, 30.28, 29.68, 29.65, 29.60, 29.53, 29.39, 29.35, 29.01, 26.51, 22.68, 14.11. HRMS (ESI): *m/z* calcd for $C_{24}H_{47}N_4O_3$ $(M+H)^+$: 439.3643, found: 439.3649.

*4.13.8. (2S,3R,4S)-4-Amino-2-(((1-octadecyl-1H-1,2,3-triazol-4-yl) methoxy)methyl)tetrahydrofuran-3-ol (**14h**)*

Yield 91%. White solid. Mp: 67–68 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm): δ 7.57 (s, 1H), 4.78–4.64 (m, 2H), 4.34 (t, *J* = 7.3 Hz, 2H), 4.05 (dd, *J* = 9.1, 5.7 Hz, 1H), 3.95–3.91 (m, 1H), 3.90–3.84 (m, 1H), 3.74 (t, *J* = 4.0 Hz, 2H), 3.65 (dd, *J* = 9.1, 4.3 Hz, 1H), 3.37 (d, *J* = 5.4 Hz, 1H), 2.64 (s, 3H), 1.98–1.81 (m, 2H), 1.36–1.22 (m, 30H), 0.89 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ 144.59, 122.44, 84.08, 79.70, 74.00, 70.72, 64.73, 59.69, 50.44, 31.92, 30.28, 29.69, 29.65, 29.61, 29.54, 29.40, 29.36, 29.01, 26.51, 22.68, 14.12. HRMS

(ESI): *m/z* calcd for $C_{26}H_{51}N_4O_3$ $(M+H)^+$: 467.3956, found: 467.3962.

### 4.14. Antiproliferative activity assays

Exponentially growing cells were seeded into 96-well plates at a concentration of $5 \times 10^3$ cells per well. After 24 h incubation at 37 °C, the culture medium was removed and replaced with fresh medium containing the candidate compounds in different concentrations. The cells were incubated for another 48 h. Afterward, 20 mL of MTT solution (5 mg/mL) was added to all wells and incubated for 4 h at 37 °C. Discarded the suspension and added 150 mL of dimethyl sulfoxide (DMSO) to each well and shook the plates to dissolve the dark blue crystals (formazan); The absorbance was measured using a microplate reader at a wavelength of 490 nm. Each concentration was analyzed in triplicate and the experiment was repeated three times. The average 50% inhibitory concentration ($IC_{50}$) was determined from the dose–response curves according to the inhibition ratio for each concentration.

### 4.15. Flow cytometric analysis of cell cycle distribution

For flow cytometric analysis of DNA content, $1 \times 10^6$ MCF-7 cells in exponential growth were treated with different concentrations of the test compounds for 8 or 16 h. After an incubation period, the cells were collected, centrifuged and fixed with icecold ethanol (75%). The cells were then treated with buffer containing RNAse A (5 ug/mL) and 1% Triton X-100 and then stained with PI (50 ug/mL) for 30 min. Samples were analyzed on Accuri C6 flow cytometer (Becton, Dickinson). Data obtained from the flow cytometer was analyzed using the FlowJo software (Tree Star, Inc., Ashland, OR, USA).

### 4.16. Flow cytometric analysis of cellular apoptosis

MCF-7 cells were plated in 6-well plates ($1 \times 10^6$ cells/mL) and incubated for 12 h. Exponentially growing cells were then incubated for 8 or 16 h with complete medium (control) or with the compound. Cells were then harvested and the Annexin-V-FITC/PI apoptosis kit (Biovision) was used according to the manufacturer's instructions to detect apoptotic cells. Ten thousand events were collected for each sample and analyzed by Accuri C6 flow cytometer.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.03.022.

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