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Original article

Biological evaluation of new mimetics of annonaceous acetogenins: Alteration of right scaffold by click linkage with aromatic functionalities

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ABSTRACT

A small library of analogues of annonaceous acetogenins through click linkage with aromatic moieties is established using a convergent modular fragment-assembly approach. These analogues exhibited low micromolar inhibitory activities against the proliferation of several human cancer cell lines. Structure–activity relationship (**SAR**) of these analogues indicates that replacement of the methoxy groups of ubiquinone ring with methyl groups is proved to be a useful strategy for improving the anticancer activity of quinone–acetogenin hybrids.

1. Introduction

Annonaceous acetogenins, a large unique family of natural polyketides with more than 400 members, have been isolated and characterized from *Annonaceous* plants growing in tropical and subtropical regions in the past three decades [1–3]. Most acetogenins exhibit a broad spectrum of bioactivity such as antitumor, immunosuppressive, antimalarial, antifeedant, and insecticidal activities, among which their antitumor activities are probably most attractive. It is generally accepted that the main mode of action of acetogenins is the blockage of complex **I** (**NADH**-ubiquinone oxidoreductase) in mitochondria [4,5]. Due to their unique chemical structures and excellent antitumor activities, annonaceous acetogenins have been attracting worldwide attention [1,2,6]. We have engaged in simplifying the structure of natural acetogenins with medicinal considerations for several years [7–15]. In our previous studies, a mimic of naturally occurring acetogenins-AA005 have been successfully developed by replacement of the THF rings of natural bullatacin with an ethylene glycol ether unit and exhibited very potent antitumor activity against a variety of human cancer cell lines in low to medium nanomolar range, whereas it had low cytotoxicity against normal human cells [8–10]. Subsequently, we also developed a new mimic **1** bearing a biphenyl moiety in the left hydrocarbon chain part, which was identified to show more potent inhibitory activity and higher selectivity against cancer cells than normal cells by comparison with AA005 [16].

The γ-lactone moiety of most natural acetogenins was suggested to probably interact with the quinone binding site of complex **I**. To clarify the mode of action of acetogenins, Koert et al. designed two hybrid analogues in which the γ-lactone moiety was replaced with the quinone portion of ubiquinone, a natural substrate of complex **I**. The hybrid analogue quinone–mucocin showed

Abbreviations: NADH, nicotinamide adenine dinucleotide; THF, tetrahydrofuran; TMS, trimethylsilyl; DCM, dichloromethane; DIPEA, Ethyldiisopropylamine; TBAF, tetrabutylammonium fluoride; MOMCl, chloromethyl methyl ether; BTEAC, benzyltriethylammonium chloride; DMF, N,N-dimethylformamide.

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10 times more potent complex **I** inhibitory activity than that of natural mucocin [17–19]. This mentioned that exchange of the γ-lactone moiety of natural acetogenins with other aromatic structural equivalents might remain the bioactivity. Click chemistry has been increasingly applied as a useful tool in biomedical research and drug discovery in the past two decades. It greatly simplifies compound synthesis, providing the means for faster lead discovery and optimization. For lead optimization, it enables rapid SAR profiling, through generating analog libraries quickly and reliably by joining small units together [20–23]. According to the structural characteristics of compound **1**, we wish to explore small focused library of annonaceous acetogenin analogues by replacing the γ-lactone moiety with various aromatic functionalities with Click chemistry (Fig. 1). Practically, generation of proper aromatic moieties in the right region of compound **1**-like molecules using two pre-functionalized fragments alkynes and azides would provide a new convergent access to this class of anticancer compounds. Herein, we report our results from this approach, by which the γ-

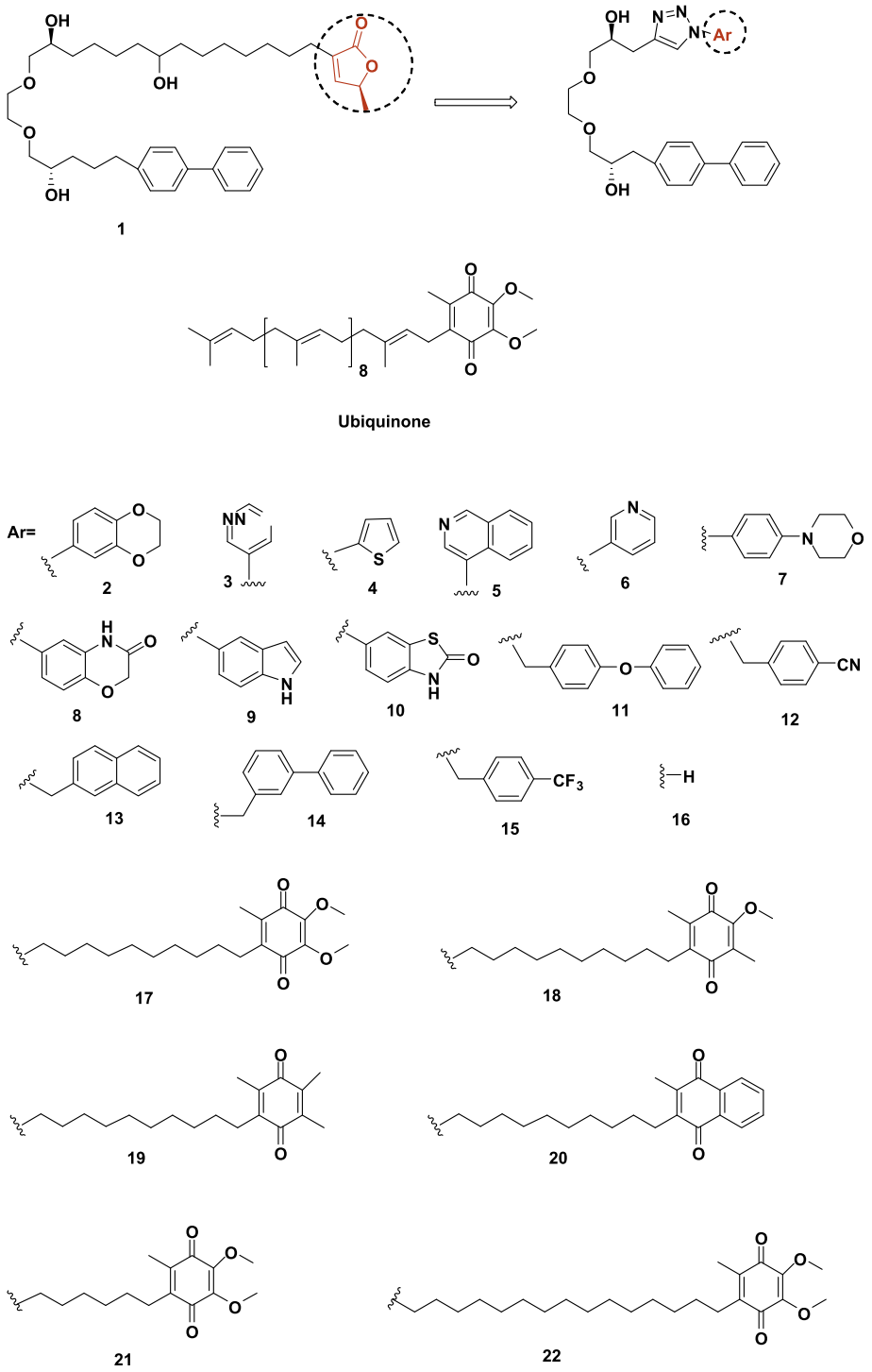


Fig. 1. Design of acetogenin analogues by click linkage with aromatic functionalities.

lactone moiety of compound **1** was replaced with diverse aromatic moieties including ubiquinone analogues and a variety of heterocycles. Among these, several analogues were found to exhibit good to excellent selectivity between human cancer cell lines and human normal cell lines.

2. Chemistry

Synthesis of the segment with a terminal alkyne was shown in Scheme 1. Mono-protection of ethylene glycol gave the corresponding benzyl ether **24**, which was further reacted with (*R*)-epichlorohydrin to afford **25** in 80% yield. Regioselective opening of epoxide **25** with the Grignard reagent derived from 4-bromobiphenyl followed by protection with MOMCl afforded **27**. Removal of the O-benzyl group of **27** by hydrogenolysis, and the newly born hydroxyl group was subsequently reacted with (*R*)-epichlorohydrin to afford **28**. Epoxide opening of **28** with the lithium salt of trimethylsilylacetylene in the presence of boron trifluoride-etherate, treatment with MOMCl and removal of TMS with TBAF afforded the first segment **29**.

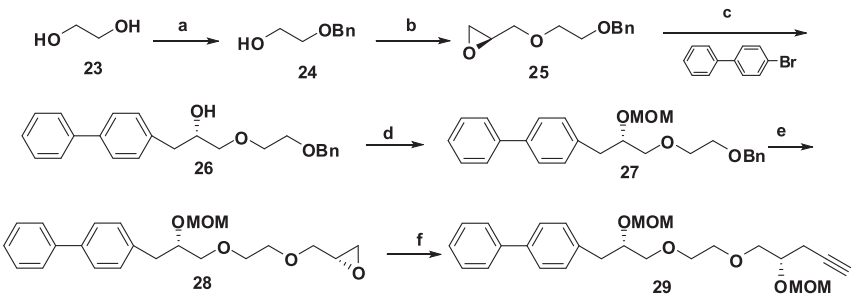
Syntheses of the azides **2b**–**15b** were shown in Scheme 2. The aryl azides **2b**–**10b** were synthesized from the corresponding aryl bromide substrates by treatment with sodium azide, sodium ascorbate, copper sulfate pentahydrate, L-proline and sodium carbonate in DMF and water. And the benzyl azides **11b**–**15b** were synthesized from the corresponding benzyl bromides via treatment with sodium azide in DMF and water.

Syntheses of ubiquinone analogues were shown in Scheme 3. The syntheses of quinone precursors **31** and **35** have been reported previously [24]. Oxidation of 2,3,5-trimethylphenol **30** afforded **31** in 90% yield. Treatment of 2,5-dimethyl-p-benzoquinone with acetic anhydride and boron trifluoride-etherate afforded **33** in 92% yield. Compound **33** was then treated with sodium hydroxide and dimethyl sulfate in methanol to provide **34** in 80% yield. Subsequently, compound **34** was oxidized using phenyliodine diacetate (PIDA), providing **35** in 60% yield. Finally, compounds **38**–**43** were synthesized, in parallel, through radical alkylation of the quinone [25] by decarboxylation of the corresponding bromo-acid with silver nitrate and ammonium persulfate. Conversion of **43** into the corresponding mesylate **44** with MsCl and triethylamine in dichloromethane followed by treatment with sodium bromide in acetone at reflux provided quinone **45** in 58% yield over two steps.

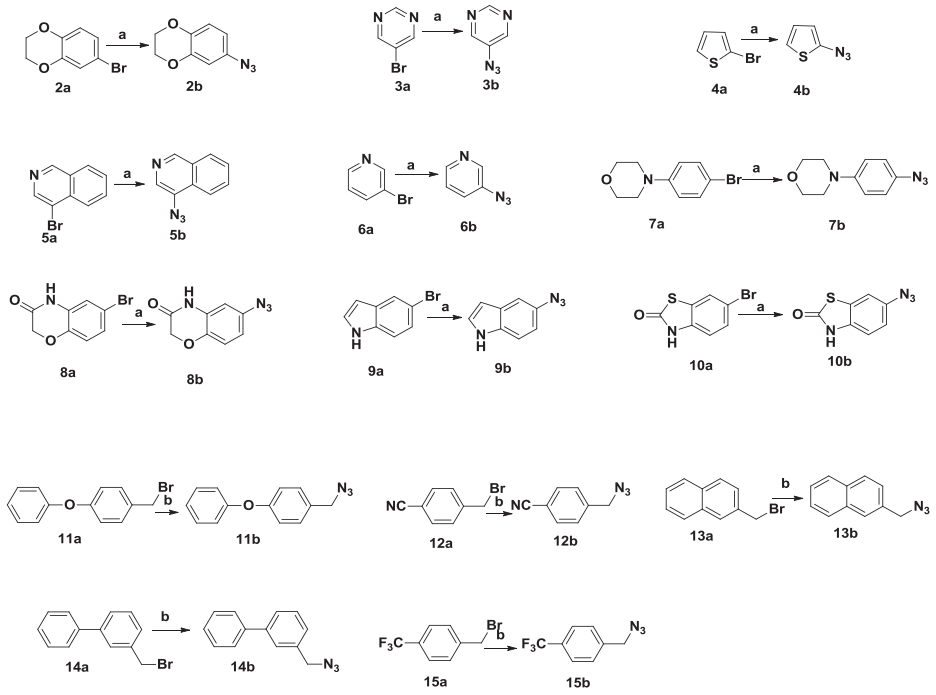
With the above three building blocks in hand, the final products could be prepared via Click chemistry (Scheme 4). The common terminal alkyne **29** was treated in parallel with azides **2b**–**15b** and sodium azide, in the presence of catalytic amount of copper sulfate and sodium ascorbate in DMF and water. The crude triazole products were then treated in parallel with dilute hydrochloric acid, giving analogues **2**–**16**. With the same terminal alkyne **29**, parallel one-pot treatment with quinones **38**–**42** and **45**, sodium azide, in the presence of catalytic amount of copper sulfate and sodium ascorbate in DMF and water, providing crude triazoles. Further treatment with pyridinium p-toluenesulfonate (PPTS) in tert-butanol gave analogues **17**–**22** in good yields, respectively.

3. Results and discussion

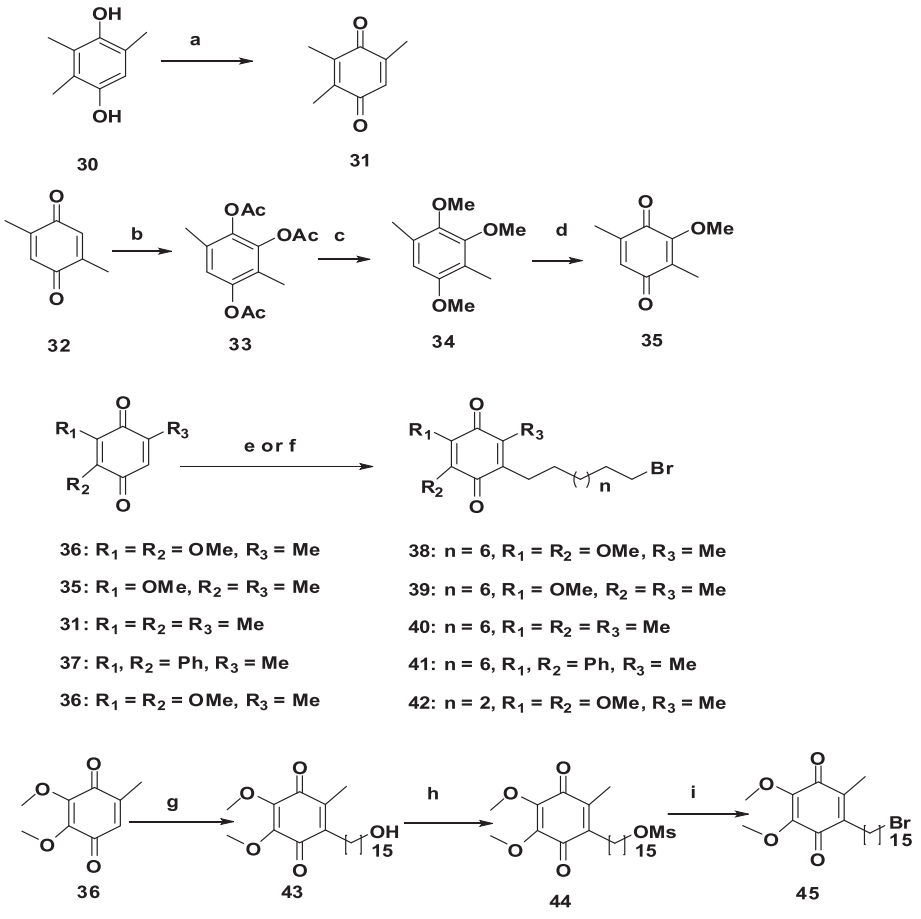
Compounds **2**–**22** were evaluated with MTT assays for their inhibitory activity against proliferation of two human solid tumor cell lines SGC7901 and HCT-116, and normal human embryonic lung fibroblasts (HLF). The results are summarized in Table 1. Most of the compounds exhibited moderate inhibitory activity against human cancer cell lines, and several compounds showed more potent inhibitory activity by comparison with adriamycin. Compound **16** lost its inhibitory activities against cancer cell lines, indicating that aromatic moieties on N1 position of 1,2,3-triazole might be essential for the anti-tumor activity. It is observed that heterocyclic rings on N1 position of 1,2,3-triazole did not improve the inhibition activity (**2**–**6**, **8**). For instance, the inhibitory activity against cancer cell lines was increased slightly when a thiophene ring was introduced at N1 position of 1,2,3-triazole. When different functional groups such as trifluoromethyl, morpholine, CN, phenyloxy or phenyl groups were introduced at para-position of the phenyl ring, the selectivities between cancerous and normal cell lines were significantly increased, suggesting that the *para*-position of the phenyl ring might be a feasible position for further optimization (**7**, **11**–**15**). To our delight, the ubiquinone ring could significantly increase inhibition activities against cancer cell lines (**17**–**20**). For example, compound **17** is 167 times more potent than compound **16** against HCT-116 cell line. To investigate the effect of methoxy group of ubiquinone ring, we replaced the methoxy group with one and two methyl groups, respectively, whereby the resulting compounds **18** and **19** showed 7 and 10 times more potent than **17** against SGC7901 cell line, respectively (**18**, GI_{50} = 0.505 μM; **19**, GI_{50} = 0.35 μM). The results indicate that replacement of the methoxy groups of ubiquinone ring by methyl groups may be a very useful strategy for the improvement of anticancer activity of these analogues. When replacing ubiquinone ring of **17** with more hydrophobic group 2-methyl-1,4-naphthoquinone, the resulting compound **20** exhibited 10 times more potent than **17** against SGC7901 cell line, indicating that ubiquinone ring maybe localizes in a hydrophobic region. To investigate the optimal length of the hydrocarbon chain between ubiquinone ring and triazole, we designed compounds **21** and **22**, whose fatty chains have 6 and 15 carbon atoms, respectively. Compound **21**, in which the hydrocarbon chain was shortened, is 4 times less potent than **17** against SGC7901 cell lines. However, compound **22**, in which the hydrocarbon chain was extended,



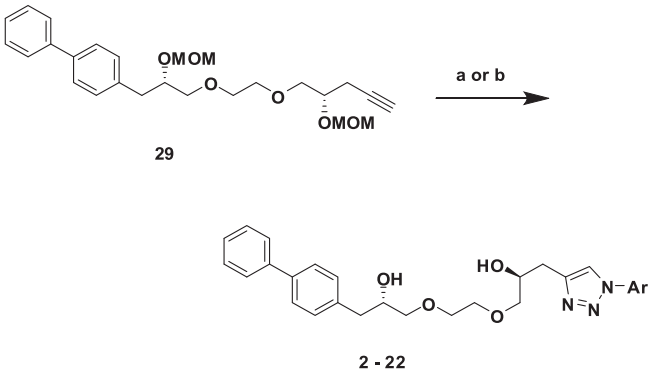
Scheme 1. Synthesis of terminal alkyne **29**[a]. [a]Reagents and conditions: (a) NaH, THF, benzyl bromide, rt-reflux, 81%. (b) (R)-epichlorohydrin, BTEAC, 50% aq. NaOH, rt, 80%. (c) Mg, THF, Red Al (cat), rt to 0 °C, 88%; (d) MOMCl, DIPEA, DCM, 0 °C to rt, 86%. (e) (i) 10% Pd/C, H_2, EtOH, HOAc, rt; (ii) (R)-Epichlorohydrin, BTEAC, 50% NaOH, rt, 85% in 2 steps. (f) (i) trimethylsilylacetylene, n-BuLi, $BF_3{\cdot}Et_2O$, THF, -78 °C; (ii) MOMCl, DIPEA, DCM, 0 °C to rt; (iii) TBAF, THF, 0 °C, 73% in 3 steps.



Scheme 2. Synthesis of azides **2b**–**15b**[a]. [a]Reagents and conditions: (a) NaN_3, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, L-Proline, Na_2CO_3, DMF/H_2O 2:1, 85 °C; (b) NaN_3, DMF/H_2O 2:1.



Scheme 3. Synthesis of ubiquinone analogues[a]. [a]Reagents and conditions: (a) I_2, H_2O_2, H_2SO_4, MeOH, 23 °C, 90%; (b) Ac_2O, $BF_3 \cdot Et_2O$, 40 °C, 92%; (c) Me_2SO_4, aq NaOH, MeOH, 23 °C, 80%; (d) PIDA, 9:1, H_2O/MeOH, 23 °C, 60%; (e) 11-bromoundecanoic acid, $AgNO_3$, $(NH_4)_2S_2O_8$, 1:1 CH_3CN/H_2O, 75 °C, 20–56%; (f) 7-Bromoheptanoic acid, $AgNO_3$, $(NH_4)_2S_2O_8$, 1:1 CH_3CN/H_2O, 75 °C, 20%; (g) 16-hydroxyhexadecanoic acid, $AgNO_3$, $(NH_4)_2S_2O_8$, 1:1 CH_3CN/H_2O, 75 °C, 25%; (h) MsCl, Et_3N, DMAP, CH_2Cl_2, 23 °C, 97%; (i) NaBr, acetone, 56 °C, 60%.



Scheme 4. Synthesis of acetogenin analogues **2**–**22**[a]. [a]Reagents and conditions: (a) (i) organic azides **2b**–**15b**, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, DMF/H_2O 2:1, 85 °C; (ii) HCl, THF, CH_3OH (2:1:2), rt. 49–81% in 2 steps; (b) (i) corresponding quinones **38**–**42** and **45**, sodium azide, sodium ascorbate, $CuSO_4 \cdot 5H_2O$, DMF/H_2O = 2:1, 85 °C; (ii) PPTS, t-BuOH, reflux, 50–75% in 2 steps.

showed equal inhibitory activity to compound **17** against SGC7901 cells. These results indicated that moderate length between ubiquinone ring and triazole is favorable for the activity.

4. Conclusion

In summary, a convergent fragment-assembly approach has been developed and successfully applied to a small library of annonaceous acetogenin analogues. A variety of aromatic moieties were introduced for the first time into the right part of these compounds, in which a triazole functionality was employed as the linkage unit using Click chemistry. Biological evaluation of these new analogues indicates that aromatic variations in the right part exhibit various effects on the cytotoxicity and cell selectivity. Compound **19**, in which two methoxy groups of ubiquinone was replaced with methyl groups, was identified to show potent inhibitory activity against a wide range of cancer cells at low micromolar range and exhibit excellent selectivity between cancer cells and normal cells. The newly developed methodology will be potentially applicable to the synthesis of additional diverse libraries of this family of anticancer compounds, and accelerate the discovery of clinically useful antitumor agents.

5. Experimental procedure

5.1. Chemistry

^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance ARX- 400 or 500 MHz. Mass spectra were performed on Kompact Axima-CFR MALDI mass spectrometers. Optical rotations were recorded on a Perkin Elmer 341 polarimeter. Anhydrous solvents were obtained as follows: THF by distillation from sodium and benzophenone; dichloromethane from CaH_2. All other solvents were reagent grade. All moisture sensitive reactions were carried out in flame dried flask under argon atmosphere.

5.1.1. General procedure for synthesis of organic azide

A: For aryl azides: Sodium ascorbate (59.4 mg, 0.3 mmol) and $CuSO_4 \cdot 5H_2O$ (23 mg, 0.12 mmol) were added to a mixture of aryl bromide (0.6 mmol), sodium azide (59.1 mg, 0.9 mmol), L-proline (13.8 mg, 0.12 mmol) and Na_2CO_3 (12.7 mg, 0.12 mmol) in 2 mL of DMF/H_2O (2:1). The mixture was stirred overnight at 85 °C. Then water (8 mL) and concentrated NH_4OH (2 mL) were added and the crude mixture was extracted with ether (10 mL × 3), then the combined organic layers were washed with saturated NH_4Cl solution and brine, dried over Na_2SO_4 (anhydrous), filtered and concentrated to give a crude azido compound, which was used as such in the subsequent step.

B: For benzyl azides: The benzyl bromide (0.6 mmol) and sodium azide (59.1 mg, 0.9 mmol) were dissolved in DMF/H_2O (2 mL, 2:1). The mixture was stirred overnight at 85 °C. Then water (8 mL) was added and the crude mixture was extracted with ether (10 mL × 3), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give a crude azido compound, which was used as such in the subsequent step.

5.1.2. 2-(Benzyloxy)ethanol (**24**)

To a mixture of sodium hydride (5.10 g, 0.17 mol, 80%, w/w) in dried THF (300 mL) was added dry ethylene glycol (50.2 mL, 0.9 mol) at room temperature over 1 h, stirred another 0.5 h, then the mixture was refluxed and benzyl bromide (17.8 mL, 0.15 mol) was added over 2 h. The mixture was refluxed for 15 h, cooled to room temperature, quenched with saturated aqueous NH_4Cl (5 mL) solution and evaporated THF under reduced pressure. The residue was extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with saturated aqueous NH_4Cl solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting oil was distilled under reduced pressure to afford **24** (18.5 g, 81%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.29 (m, 5H), 4.57 (s, 2H), 3.78–3.74 (m, 2H), 3.62–3.59 (m, 2H), 2.10 (br, 1H, OH) ppm.

5.1.3. (S)-2-((2-(benzyloxy)ethoxy)methyl)oxirane (**25**)

To a solution of **24** (10.7 g, 0.07 mol) was added BTEAC (1.60 g, 15%, w/w) and (*R*)-(−)-epichlorohydrin (6.6 mL, 0.084 mol), stirred for 3 min, then a solution of 50% NaOH (55 mL) was added over 0.5 h. The reaction mixture was vigorously stirred at room temperature for another 3.5 h, and then the solution was quenched by water (40 mL). The resulting solution was extracted by ether (40 mL × 3), washed successfully by saturated aqueous NH_4Cl solution and brine. The organic phase was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The resulting mixture was purified by silica gel column chromatography to give **25** (11.7 g, 80%) as a colorless oil. $[\alpha]^2 5_D$: 6.1 (*c* 2.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.27 (m, 5H), 4.58 (s, 2H), 3.80 (dd, J = 11.6, 3.0 Hz, 1H), 3.75–3.63 (m, 4H), 3.45 (dd, J = 11.6, 5.8 Hz, 1H), 3.18–3.16 (m, 1H), 2.80–2.78 (m, 1H), 2.62 (dd, J = 5.0, 2.7 Hz, 1H) ppm; HRMS (ESI): $C_{12}H_{16}O_3$ calculated $[M + H]^+$ 209.1172, found 209.1175, $[M + Na]^+$ 231.0992, found 231.0990.

5.1.4. (S)-1-(2-(benzyloxy)ethoxy)-3-(biphenyl-4-yl)propan-2-ol(**26**)

A solution of the epoxide **25** (4.10 g, 19.7 mmol) in anhydrous of THF (30 mL) was added slowly to a solution of biphenyl-4-ylmagnesium bromide (freshly prepared from 4-bromobiphenyl) (7.02 g, 29.55 mmol) and Mg turnings (1.45 g, 59.1 mmol) in dry anhydrous THF (60 mL) in the presence of CuBr (0.42 g, 2.96 mmol) at 0 °C. After stirred for 1 h at 0 °C, the reaction mixture was stirred at room temperature for another 3 h. Then saturated NH_4Cl (10 mL) was added to quench the reaction, and the mixture was stirred for additional 15 min. Evaporated THF under reduced pressure. The residue was extracted with ether (30 mL × 3). The combined organic layers were washed with saturated aqueous NH_4Cl solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting mixture was purified by silica gel column chromatography to give **26** (6.30 g, 88% for 2 steps) as a white solid. $[\alpha]_{25}D$: 4.9 (*c* 0.75, CHCl3). ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 7.5 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.44 (dd, J = 7.6 Hz, 2H), 7.35–7.28 (m, 8H), 4.58 (s, 2H), 4.12–4.06 (m, 1H),

Table 1
Antiproliferative activity of AA005 and analogues 2–22.[a]

Compounds	GI_{50}(μM)		
	HCT116	SGC7901	HLF
2	16.5	6.4	5.2
3	>100	>100	>100
4	33.4	33.4	>100
5	17.8	29.3	10.8
6	46.8	29.8	>100
7	8.3	20.7	>100
8	42.5	15.2	>100
9	15.5	45.6	>100
10	9.2	10.5	47.7
11	3.4	4.5	22.8
12	8.8	7.7	36.6
13	8.6	12.1	19.8
14	7.2	10.6	>100
15	2.5	8.7	29.8
16	>100	>100	>100
17	0.6	3.8	18.3
18	4	0.505	35.1
19	0.9	0.35	>25
20	3	0.39	22.6
21	5	16.65	>50
22	1.5	2.49	>50
Adriamycin	0.15	0.55	0.33
AA005	0.181	0.076	27.8

[a] Adriamycin and AA005 were used as positive control. HCT116: colorectal carcinoma cell line; SGC7901: human gastric cancer cell line; HLF: normal human lung fibroblasts. Inhibition of cell growth by the listed compounds was determined by using MTT assay. Standard error of the GI_{50} was generally less than 10%.

3.72–3.68 (m, 2H), 3.67–3.63 (m, 2H), 3.58 (dd, J = 9.8, 3.2 Hz, 1H), 3.57 (dd, J = 9.8, 3.2 Hz, 1H), 2.89–2.79 (m, 2H), 2.66 (d, J = 3.7 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0, 139.4, 138.2, 137.2, 129.7, 128.7, 128.4, 127.7, 127.2, 127.1, 127.0, 74.8, 73.3, 71.3, 70.8, 69.5, 39.5 ppm. MS (ESI, *m/z*): 363 (M^+ + 1), 385 (M^+ + 23).

5.1.5. (S)-5-(biphenyl-4-ylmethyl)-11-phenyl-2,4,7,10-tetraoxaundecane (**27**)

The alcohol **26** (6.21 g, 17.1 mmol) was dissolved in dry DCM (70 mL) under nitrogen atmosphere, DIPEA (20.8 mL, 119.7 mmol) was added, the reaction mixture was cooled to 0 °C. MOMCl (6.50 mL, 8 5.5 mmol) was added slowly, and the reaction mixture was stirred at ambient temperature for 20 h. Then the mixture was quenched by saturated NH_4Cl (10 mL) solution and evaporated DCM under reduced pressure. The residue was extracted with ether (30 mL × 3). Then the combined organic layers were washed with saturated NH_4Cl solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to leave an oil. Purification by silica gel column chromatography afforded **27** (5.99 g, 86%) as a colorless oil. $[\alpha]_{25}D$: 1.3 (c 0.90, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 7.3 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.44 (dd, J = 7.6 Hz, 2H), 7.37–7.29 (m, 8H), 4.74 (d, J = 6.8 Hz, 1H), 4.61–4.60 (m, 3H), 4.03 (m, 1H), 3.71–3.66 (m, 4H), 3.57–3.55 (m, 2H), 3.23 (s, 3H), 2.98–2.91 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.1, 139.2, 138.4, 137.6, 130.0, 128.7, 128.4, 127.7, 127.6, 127.1, 127.0, 76.9, 73.3, 73.1, 70.9, 69.6, 55.3, 38.1 ppm. MS (ESI, *m/z*): 407 (M^+ + 1), 429 (M^+ + 23).

5.1.6. (S)-2-((S)-5-(biphenyl-4-ylmethyl)-2,4,7,10-tetraoxaundecan-11-yl)oxirane (**28**)

A mixture of **27** (5.88 g, 14.5 mmol), 10% palladium on charcoal (0.59 g), and EtOH (50 mL, containing 3 mL HOAc) was stirred at room temperature for 20 h under hydrogen atmosphere. After removal the solid phase, the organic phase was concentrated. The residue was used in the next step without purification.

To the above intermediate was added BTEAC (0.69 g, 15%, w/w) and (R)-(−)-epichlorohydrin (1.36 mL, 17.4 mmol), stirred for 3 min, then a solution of 50% NaOH (12.0 mL) was added over 15 min. The reaction mixture was vigorously stirred at room temperature for another 22 h, and then the solution was quenched by water (20 mL). The resulting solution was extracted by ether (20 mL × 3), washed successfully by saturated NH_4Cl solution and brine. The organic phase was dried over Na_2SO_4 (anhydrous), filtered and concentrated. Purification by silica gel column chromatography afforded **28** as a colorless liquid (4.58 g, 85% for 2 steps). $[\alpha]_{25}D$: 1.4 (c 1.18, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 7.4 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.43 (dd, J = 7.6 Hz, 2H), 7.35–7.31 (m, 3H), 4.72 (d, J = 6.8 Hz, 1H), 4.59 (d, J = 6.8 Hz, 1H), 4.01 (m, 1H), 3.80 (dd, J = 11.6, 2.9 Hz, 1H), 3.72–3.62 (m, 4H), 3.54 (m, 2H), 3.47–3.42 (m, 1H), 3.22(s, 3H), 3.16 (m, 1H), 2.97–2.85 (m, 2H), 2.80–2.78 (m, 1H), 2.62–2.60 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 139.1, 137.4, 129.9, 128.6, 127.0, 126.8, 95.8, 76.8, 73.0, 71.9, 71.8, 70.7, 55.2, 50.7, 44.0, 37.9 ppm. MS (ESI, *m/z*): 373 (M^+ + 1), 395 (M^+ + 23), HRMS (ESI): $C_{22}H_{28}O_5$ calculated $[M + H]^+$ 395.1829, found 395.1826.

5.1.7. (5S,12S)-5-(biphenyl-4-ylmethyl)-12-(prop-2-ynyl)-2,4,7,10,13,15-hexaoxahexadecane (**29**)

To a solution of trimethylsilylacetylene (6.95 mL, 46 mmol) in dried THF (45 mL) was added slowly n-BuLi (29 mL, 46 mmol, 1.6 M in hexane) at −78 °C. The reaction mixture was stirred for 45 min at −78 °C under argon atmosphere, and $BF_3 \cdot Et_2O$ (5.8 mL, 46 mmol) was added, and stirred for another 30 min. Then a solution of **28** (4.30 g, 11.5 mmol) in dried THF (25 mL) was added, and the reaction mixture was stirred for another 3 h. The solution was quenched by saturated $NaHCO_3$ (5 mL) solution and evaporated THF under reduced pressure. The residue was extracted with ether (20 mL × 3). Then the combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to leave an oil, which was used in the next step.

The crude product was dissolved in dry DCM (60 mL) under nitrogen atmosphere. Then DIPEA (14 mL, 80.5 mmol) was added, and the reaction mixture was cooled to 0 °C. MOMCl (4.4 mL, 57.5 mmol) was added slowly, and the reaction mixture was stirred at ambient temperature for 24 h. Then the mixture was quenched by saturated NH_4Cl (10 mL) solution and evaporated under reduced pressure. The residue was extracted with ethyl acetate (25 mL × 3). Then the combined organic layers were washed with saturated NH_4Cl solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to leave an oil, which was used as such in the subsequent synthesis step.

The above intermediate was dissolved in THF (25 mL), cooled to −10 °C, then TBAF (13.8 mmol, 1.0 M in THF) was added to the solution, stirred for 3 h at −10 °C. The mixture was quenched by saturated NH_4Cl (5 mL) solution and evaporated THF under reduced pressure. The residue was extracted with ether (20 mL × 3). Then the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Purification by silica gel column chromatography afforded **29** as a yellow oil (3.71 g, 73% for 3 steps). $[\alpha]_{25}D$: 2.2 (c 5.72, $CHCl_3$). ^{1}H NMR (400 MHz, CDCl3): δ 7.59 (d, J = 7.4 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.43 (dd, J = 7.6 Hz, 2H), 7.35–7.31 (m, 3H), 4.74 (m, 2H), 4.72 (d, J = 6.8 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 3.99 (m, 1H), 3.89 (m, 1H), 3.69–3.61 (m, 6H), 3.53–3.51 (m, 2H), 3.40 (s, 3H), 3.22(s, 3H), 2.98–2.85 (m, 2H), 2.59–2.45 (m, 2H), 1.99 (t, J = 2.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, CDCl3): δ 141.0, 139.1, 137.5, 129.9, 128.6, 127.0, 126.9, 96.0, 95.8, 80.6, 76.8, 74.3, 73.0, 72.4, 70.9, 70.7, 69.9, 55.4, 55.2, 38.0, 21.8 ppm. MS (ESI, *m/z*): 465 (M^+ + 23), HRMS (ESI): $C_{26}H_{34}O_6$ calculated $[M + Na]^+$ 465.2248, found 465.2248.

*5.1.8. Trimethyl-p-benzoquinone (**31**)*

To a stirred solution containing (1.00 g, 6.57 mmol) of trimethyl-p-hydroquinone **30** in 20 mL of methanol at 23 °C were added (83.3 mg, 0.33 mmol) of iodine followed by (329 uL, 2.90 mmol) of 30% aq hydrogen peroxide and (329 uL, 0.93 mmol) of sulfuric acid. The reaction mixture was stirred at 23 °C for 3 h and was then diluted with 150 mL of ether. The organic layer was washed with three 75-mL portions of water, then with one 75-mL portion of satd aq sodium thiosulfate and then with 75 mL of brine. The organic layer was dried ($MgSO_4$) and concentrated under diminished pressure to afford trimethyl-p-benzoquinone **31**(887 mg, 90%) as yellow crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.52 (s, 1H), 2.00 (m, 9H).

*5.1.9. 1,2,4-Triacetoxy-3,6-dimethylbenzene (**33**)*

To stirred solution of 2,5-dimethyl-p-benzoquinone **32** (1.00 g, 7.34 mmol) in acetic anhydride (8.0 mL) at 23 °C was added boron trifluoride etherate (400 uL, 3.13 mmol). The reaction mixture was stirred at 40 °C for 48 h and then poured into water (100 mL). The formed precipitate was collected by filtration, and then dried under reduced pressure to afford **33** (1.89 g, 92%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 (s, 1H), 2.29 (s, 9H), 2.15 (s, 3H), 1.96 (s, 3H) ppm.

*5.1.10. 3,6-Dimethyl-1,2,4-trimethoxybenzene (**34**)*

To a stirred solution of **33** (1.8 g, 6.43 mmol) in methanol (6.0 mL) were added dimethyl sulfate (5.0 mL, 52.3 mmol) followed by the slow addition of a solution of sodium hydroxide (2.17 g, 54.3 mmol) in water (2.5 mL) at 25 °C. The reaction mixture was stirred at 23 °C for 16 h. The reaction mixture was poured into water (60 mL) and then extracted with diethyl ether/hexanes (80 mL, 1:1) and then with hexanes (60 mL). The combined organic layer was washed with water (80 mL) and brine (80 mL). The solution was dried with $MgSO_4$ and then concentrated under reduced pressure. The resulting mixture was purified by silica gel column chromatography to give **34** (1 g, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (s, 1H), 3.83 (s, 3H), 3.78 (s, 6H), 2.26 (s, 3H), 2.11 (s, 3H) ppm.

*5.1.11. 3,6-Dimethyl-2-methoxy-p-benzoquinone (**35**)*

To a stirred solution of **34** (900 mg, 4.59 mmol) in water/methanol (30 mL, 9:1) at 23 °C was added phenyliodine diacetate (PIDA) (2.21 g, 6.86 mmol). The reaction mixture was stirred at 40 °C for 16 h, and then poured into water (100 mL). The product was extracted with ether (2 × 75 mL). The organic layer was washed with water (100 mL), then with sat. aq sodium bicarbonate solution (100 mL) and brine (100 mL). The organic phase was dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting mixture was purified by silica gel column chromatography to give **35** (457 mg, 60%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.52 (s, 1H), 3.98 (s, 3H), 2.03 (s, 3H), 1.93 (s, 3H) ppm.

*5.1.12. 2-(10-Bromodecyl)-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**38**)*

A solution of $(NH_4)_2S_2O_8$ (1.4 g, 6 mmol) in water (30 mL) was added dropwise over 1 h to a stirred suspension of **36** (0.91 g, 5 mmol), $AgNO_3$ (0.85 g, 5 mmol) and 11-Bromoundecanoic acid (1.5 g, 5.5 mmol) in CH_3CN (30 mL) and water (30 mL) at 75 °C. The reaction mixture was stirred at 75 °C for 4 h in the dark and was then cooled to 23 °C, the mixture was extracted with diethyl ether, then washed with saturated aqueous $NaHCO_3$ and brine. The ether phase was dried over anhydrous $MgSO_4$ and filtered, and then the solvent was removed in vacuo at room temperature. The resulting mixture was purified by silica gel column chromatography to give **38** (0.4 g, 20%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 6H), 3.38 (t, J = 6.8 Hz, 2H), 2.43 (t, J = 6.8 Hz, 2H), 1.99 (s, 3H), 1.85–1.81 (m, 2H), 1.42–1.18 (m, 14H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.1, 184.0, 155.5, 144.7, 138.5, 128.6, 60.8, 34.0, 32.8, 29.9, 29.4, 29.3, 28.8, 28.7, 28.1, 26.7, 11.7 ppm. MS (ESI, m/z): 401 ($M^+ + 1$).

*5.1.13. 2-(10-Bromodecyl)-5-methoxy-3,6-dimethylcyclohexa-2,5-diene-1,4-dione (**39**)*

The procedure was the same as described above for the synthesis of **38**, the compound **39** was obtained as yellow solid (0.5 g, 26%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (s, 3H), 3.40 (t, J = 6.8 Hz, 2H), 2.45 (t, J = 6.8 Hz, 2H), 2.01 (s, 3H), 1.93 (s, 3H), 1.85 (quint, J = 6.8 Hz, 2H), 1.39–1.25 (m, 14H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.1, 184.0, 155.5, 144.7, 138.5, 128.6, 60.8, 34.0, 32.8, 29.9, 29.4, 29.3, 28.8, 28.7, 28.1, 26.7, 11.7, 8.8 ppm. MS (ESI, m/z): 385 ($M^+ + 1$).

*5.1.14. 2-(10-Bromodecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (**40**)*

The procedure was the same as described above for the synthesis of **38**, the compound **40** was obtained as yellow solid (0.4 g, 22%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40 (t, J = 6.8 Hz, 2H), 2.45 (t, J = 6.8 Hz, 2H), 2.00 (s, 9H), 1.84 (quint, J = 6.8 Hz, 2H), 1.43–1.25 (m, 14H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.8, 187.2, 144.5, 140.4, 140.3, 140.0, 34.0, 32.8, 29.9, 29.37, 29.36, 29.32, 28.8, 28.7, 28.1, 26.6, 12.3, 12.1 ppm. MS (ESI, m/z): 369 ($M^+ + 1$).

*5.1.15. 2-(10-Bromodecyl)-3-methylnaphthalene-1,4-dione (**41**)*

The procedure was the same as described above for the synthesis of **38**, the compound **41** was obtained as yellow solid (1.1 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.08–8.06 (m, 2H), 7.69–7.67 (m, 2H), 3.40 (t, J = 6.8 Hz, 2H), 2.62 (t, J = 6.8 Hz, 2H), 2.19 (s, 3H), 1.84 (quint, J = 6.8 Hz, 2H), 1.49–1.29 (m, 14H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 185.4, 184.7, 147.5, 143.1, 133.3, 132.2, 132.17, 126.3, 126.2, 34.0, 32.8, 29.9, 29.4, 29.3, 28.7, 28.1, 27.1, 12.6 ppm. MS (ESI, m/z): 391 ($M^+ + 1$).

*5.1.16. 2-(6-Bromohexyl)-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**42**)*

A solution of $(NH_4)_2S_2O_8$ (1.4 g, 6 mmol) in water (30 mL) was added dropwise over 1 h to a stirred suspension of **36** (0.91 g, 5 mmol), $AgNO_3$ (0.85 g, 5 mmol) and 7-Bromoheptanoic acid (1.1 g, 5.5 mmol) in CH_3CN (30 mL) and water (30 mL) at 75 °C. The reaction mixture was stirred at 75 °C for 4 h in the dark and was then cooled to 23 °C, the mixture was extracted with diethyl ether, then washed with saturated aqueous $NaHCO_3$ and brine. The ether phase was dried over anhydrous $MgSO_4$ and filtered, and then the solvent was removed in vacuo at room temperature. The resulting mixture was purified by silica gel column chromatography to give **42** (0.35 g, 20%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 6H), 3.40 (t, J = 6.8 Hz, 2H), 2.45 (t, J = 6.8 Hz, 2H), 2.00 (s, 3H), 1.88 (quint, J = 6.8 Hz, 2H), 1.47–1.36 (m, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.6, 184.1, 144.3, 142.7, 138.8, 61.1, 33.8, 32.6, 28.9, 28.4, 27.8, 26.2, 11.9 ppm. MS (ESI, m/z): 345 ($M^+ + 1$).

*5.1.17. 2-(15-Hydroxypentadecyl)-3-methyl-5,6-dimethoxy-1,4-benzoquinone (**43**)*

A solution of $(NH_4)_2S_2O_8$ (1.4 g, 6 mmol) in water (30 mL) was added dropwise over 1 h to a stirred suspension of **36** (0.91 g, 5 mmol), $AgNO_3$ (0.85 g, 5 mmol) and 16-hydroxyhexadecanoic acid (1.5 g, 5.5 mmol) in CH_3CN (30 mL) and water (30 mL) at 75 °C. The reaction mixture was stirred at 75 °C for 4 h in the dark and was then cooled to 23 °C. The mixture was extracted with diethyl ether, then washed with saturated aqueous $NaHCO_3$ and brine. The ether phase was dried over anhydrous $MgSO_4$ and filtered, and then the solvent was removed in vacuo. The resulting

mixture was purified by silica gel column chromatography to give **43** (510 mg, 25%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (s, 6H), 3.62 (t, J = 6.8 Hz, 2H), 2.43 (t, J = 6.8 Hz, 2H), 1.99 (s, 3H), 1.55 (quint, J = 6.8 Hz, 2H), 1.33–1.24 (m, 24H) ppm.

*5.1.18. 2-(15-Methanesulfoxypentadecyl)-3-methyl-5,6-dimethoxy-1,4-benzoquinone (**44**)*

To a stirred solution of **43** (91.8 mg, 0.225 mmol), triethylamine (70.0 uL, 0.502 mmol), and dimethylaminopyridine (3.1 mg, 0.025 mmol) in dichloromethane (0.5 mL) was added methanesulfonyl chloride (21.0 uL, 0.271 mmol) at 23 °C. After stirring at 23 °C for 1 h, the reaction mixture was diluted with ether (5 mL) and then poured into a separatory funnel containing distilled water (5 mL). The organic layers were separated and the aqueous layer was extracted with ether (2 × 5 mL). The combined organic layer was washed with 0.5 M aq sodium bicarbonate (2 × 3 mL), then brine. The dried ($MgSO_4$) organic layer was then concentrated under reduced pressure to afford **44** (107 mg, 97%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.22 (t, J = 6.8 Hz, 2H), 3.99 (s, 6H), 3.00 (s, 3H), 2.44 (t, J = 6.8 Hz, 2H), 2.00 (s, 3H), 1.75 (quint, J = 6.8 Hz, 2H), 1.40–1.25 (m, 24H) ppm.

*5.1.19. 2-(15-Bromopentadecyl)-3-methyl-5,6-dimethoxy-1,4-benzoquinone (**45**)*

A solution of **44** (58.0 mg, 0.119 mmol) and sodium bromide (123 mg, 1.19 mmol) in acetone (1.2 mL) was stirred at reflux for 6.5 h. The acetone was concentrated under reduced pressure; The resulting mixture was purified by silica gel column chromatography to give **45** (34 mg, 60%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 6H), 3.39 (t, J = 6.8 Hz, 2H), 2.43 (t, J = 6.8 Hz, 2H), 2.00 (s, 3H), 1.84 (quint, J = 6.8 Hz, 2H), 1.40–1.25 (m, 24H) ppm.

*5.1.20. (S)-1-(biphenyl-4-yl)-3-(2-((S)-3-(1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1H-1,2,3-triazol-4-yl)-2-hydroxypropoxy)ethoxy)propan-2-ol (**2**)*

Compound **29** (88.5 mg, 0.2 mmol), sodium ascorbate (15.8 mg, 0.08 mmol) $CuSO_4 \cdot 5H_2O$ (9.9 mg, 0.04 mmol) and appropriate azide (0.6 mmol) were suspended in DMF/H_2O (2 mL, 2:1). The mixture was stirred overnight at 85 °C. Then water (8 mL) was added and the crude mixture was extracted with ethyl acetate (10 mL × 3), the combined organic layers were washed with brine, dried over Na_2SO_4 (anhydrous), filtered and concentrated to give a crude compound, which was used as such in the subsequent step.

The crude product obtained was then dissolved in a solution of THF and CH_3OH (1.2 mL, V/V, 1:2), added 6 N HCl (0.8 mL), stirred for 3 h at room temperature. The solution was quenched by saturated $NaHCO_3$ (3 mL) solution, extracted with ethyl acetate (10 mL × 3). Then the combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 (anhydrous), filtered and concentrated to leave an oil. Purification by silica gel column chromatography afforded **2** as a pale yellow solid (96.2 mg, 73% for 2 steps). $[\alpha]_{25}D$: 2.8 (c 0.46, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.55 (d, J = 7.6 Hz, 2H), 7.50 (d, J = 7.9 Hz, 2H), 7.41 (dd, J = 7.5 Hz, 2H), 7.33–7.27 (m, 3H), 7.23 (d, J = 2.4 Hz, 1H), 7.14 (dd, J = 8.7, 2.4 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 4.26 (s, 4H), 4.16 (m, 1H), 4.06 (m, 1H), 3.68–3.42 (m, 9H), 2.98–2.92 (m, 2H), 2.83–2.80 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 144.1, 143.9, 140.9, 139.3, 137.2, 131.0, 129.8, 128.7, 127.1, 127.0, 120.6, 117.9, 113.6, 110.1, 74.8, 71.3, 70.7, 70.6, 69.6, 64.4, 64.3, 39.5, 29.7 ppm. MS (ESI, m/z): 532 (M^+ + 1), 554 (M^+ + 23), HRMS (ESI): $C_{30}H_{33}N_3O_6$ calculated $[M + H]^+$ 532.2442, found 532.2444.

*5.1.21. (S)-1-(biphenyl-4-yl)-3-(2-((S)-2-hydroxy-3-(1-(pyrimidin-5-yl)-1H-1,2,3-triazol-4-yl)propoxy)ethoxy)propan-2-ol (**3**)*

The procedure was the same as described above for the synthesis of **2**; the compound **3** was obtained as white solid (56.7 mg, 58% for 2 steps). $[\alpha]_{25}D$: 6.6 (c 0.21, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 9.15 (s, 2H), 8.03 (s, 1H), 7.55–7.53 (m, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.41 (dd, J = 7.6 Hz, 2H), 7.33–7.27 (m, 3H), 4.16 (m, 1H), 4.07 (m, 1H), 3.73–3.40 (m, 9H), 3.06–2.92 (m, 2H), 2.86–2.78 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 148.3, 146.3, 140.8, 139.4, 137.1, 132.2, 129.7, 128.7, 127.2, 127.1, 126.9, 120.3, 74.9, 74.8, 71.3, 70.7, 70.6, 69.3, 39.5, 29.6 ppm. MS (ESI, m/z): 476 (M^+ + 1), 498 (M^+ + 23), HRMS (ESI): $C_{26}H_{29}N_5O_4$ calculated $[M + H]^+$ 476.2292, found 476.2291.

*5.1.22. (S)-1-(biphenyl-4-yl)-3-(2-((S)-2-hydroxy-3-(1-(thiophen-2-yl)-1H-1,2,3-triazol-4-yl)propoxy)ethoxy)propan-2-ol (**4**)*

The procedure was the same as described above for the synthesis of **2**; the compound **4** was obtained as white solid (46.1 mg, 57% for 2 steps). $[\alpha]_{25}D$: 7.1 (c 0.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.56 (d, J = 7.3 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.42 (dd, J = 7.6 Hz, 2H), 7.34–7.28 (m, 3H), 7.17 (d, J = 4.8 Hz, 2H), 6.98 (dd, J = 5.0 Hz, 1H), 4.16 (m, 1H), 4.08 (m, 1H), 3.67–3.40 (m, 8H), 3.01–2.91 (m, 2H), 2.86–2.79 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 140.9, 139.4, 138.6, 137.1, 129.7, 128.7, 127.1, 127.0, 126.2, 122.5, 121.7, 117.8, 74.8, 74.7, 71.3, 70.7, 70.6, 69.5, 39.4, 29.5 ppm. MS (ESI, m/z): 480 (M^+ + 1), 502 (M^+ + 23), HRMS (ESI): $C_{26}H_{29}N_3O_4S$ calculated $[M + H]^+$ 480.1952, found 480.1954.

*5.1.23. (S)-1-(biphenyl-4-yl)-3-(2-((S)-2-hydroxy-3-(1-(isoquinolin-4-yl)-1H-1,2,3-triazol-4-yl)propoxy)ethoxy)propan-2-ol (**5**)*

The procedure was the same as described above for the synthesis of **2**; the compound **5** was obtained as white solid (63.0 mg, 61% for 2 steps). $[\alpha]_{25}D$: 9.7 (c 0.36, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.31 (s, 1H), 8.60 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.76–7.67 (m, 2H), 7.52 (d, J = 7.4 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.39 (dd, J = 7.6 Hz, 2H), 7.31 (d, J = 7.3 Hz, 1H), 7.27–7.25 (m, 2H), 4.25 (m, 1H), 4.07 (m, 1H), 3.75–3.65 (m, 6H), 3.58–3.54 (m, 2H), 3.45–3.41 (m, 1H), 3.13–2.99 (m, 2H), 2.86–2.78 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 145.0, 140.8, 139.3, 139.0, 137.2, 132.3, 130.9, 129.8, 129.2, 128.9, 128.7, 128.5, 127.8, 127.1, 126.9, 124.8, 121.9, 74.9, 71.3, 70.7, 70.6, 69.5, 39.5, 29.7 ppm. MS (ESI, m/z): 525 (M^+ + 1), 547 (M^+ + 23), HRMS (ESI): $C_{27}H_{30}N_4O_4$ calculated $[M + H]^+$ 525.2496, found 525.2498, $[M + Na]^+$ 546.2316, found 547.2318.

*5.1.24. (S)-1-(biphenyl-4-yl)-3-(2-((S)-2-hydroxy-3-(1-(pyridin-3-yl)-1H-1,2,3-triazol-4-yl)propoxy)ethoxy)propan-2-ol (**6**)*

The procedure was the same as described above for the synthesis of **2**; the compound **6** was obtained as white solid (38.5 mg, 52% for 2 steps). $[\alpha]_{25}D$: 5.3 (c 0.37, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (s, 1H), 8.67 (d, J = 4.2 Hz, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.98 (s, 1H), 7.55 (d, J = 7.2 Hz, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.46–7.40 (m, 3H), 7.34–7.28 (m, 3H), 4.20 (m, 1H), 4.10 (m, 1H), 3.72–3.44 (m, 9H), 3.08–3.00 (m, 2H), 2.90–2.82 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.7, 145.7, 145.6, 141.5, 140.8, 139.4, 137.0, 133.7, 129.7, 128.7, 128.5, 127.9, 127.2, 126.9, 124.2, 120.5, 74.8, 74.7, 71.3, 70.6, 70.5, 69.5, 39.3, 29.5 ppm. MS (ESI, m/z): 475 (M^+ + 1), 497 (M^+ + 23), HRMS (ESI): $C_{27}H_{30}N_4O_4$ calculated $[M + H]^+$ 475.2340, found 475.2338.

*5.1.25. (S)-1-(biphenyl-4-yl)-3-(2-((S)-2-hydroxy-3-(1-(4-morpholinophenyl)-1H-1,2,3-triazol-4-yl)propoxy)ethoxy)propan-2-ol (**7**)*

The procedure was the same as described above for the synthesis of **2**; the compound **7** was obtained as white solid (65.4 mg,

74% for 2 steps). $[\alpha]_{25}D$: 2.6 (c 0.55, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.56–7.54 (m, 4H), 7.51 (d, J = 8.1 Hz, 2H), 7.41 (dd, J = 7.6 Hz, 2H), 7.34–7.27 (m, 3H), 6.92 (d, J = 9.0 Hz, 2H), 4.16 (m, 1H), 4.07 (m, 1H), 3.85 (t, J = 4.8 Hz, 4H), 3.69–3.40 (m, 9H), 3.23 (m, 1H), 3.16 (t, J = 4.8 Hz, 4H), 3.03–2.89 (m, 2H), 2.87–2.78 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 144.9, 140.9, 139.3, 137.3, 129.8, 129.6, 128.8, 127.1, 127.0, 121.6, 120.4, 115.7, 74.9, 74.8, 71.3, 70.6, 69.6, 66.7, 48.8, 39.4, 29.7 ppm. MS (ESI, m/z): 559 (M^+ + 1). HRMS (ESI): $C_{32}H_{38}N_4O_5$ calculated $[M + H]^+$ 559.2915, found 559.2913.

5.1.26. 6-(4-((S)-3-(2-((S)-3-(biphenyl-4-yl)-2-hydroxypropoxy) ethoxy)-2-hydroxypropyl)-1H-1,2,3-triazol-1-yl)-2H-benzo[b] [1,4] oxazin-3(4H)-one (**8**)

The procedure was the same as described above for the synthesis of **2**; the compound **8** was obtained as white solid (42.4 mg, 56% for 2 steps). $[\alpha]_{25}D$: 6.0 (c 0.27, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.56–7.54 (m, 3H), 7.51 (d, J = 8.1 Hz, 2H), 7.42 (dd, J = 7.6 Hz, 2H), 7.34–7.27 (m, 4H), 7.22 (dd, J = 8.7, 2.4 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 4.62 (s, 2H), 4.15 (m, 1H), 4.06 (m, 1H), 3.71–3.42 (m, 9H), 3.06–2.91 (m, 2H), 2.87–2.77 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.2, 145.0, 143.4, 140.6, 139.1, 136.9, 131.7, 129.5, 128.5, 127.6, 126.9, 126.7, 120.6, 117.1, 114.8, 108.5, 74.6, 71.0, 70.3, 69.1, 66.9, 39.2, 29.4 ppm. MS (ESI, m/z): 545 (M^+ + 1). HRMS (ESI): $C_{30}H_{32}N_4O_6$ calculated $[M + H]^+$ 545.2395, found 545.2393.

5.1.27. (S)-1-(1-(1H-indol-5-yl)-1H-1,2,3-triazol-4-yl)-3-(2-((S)-3-(biphenyl-4-yl)-2-hydroxypropoxy)ethoxy)propan-2-ol (**9**)

The procedure was the same as described above for the synthesis of **2**; the compound **9** was obtained as pale yellow solid (32.0 mg, 59% for 2 steps). $[\alpha]_{25}D$: 4.9 (c 0.51, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.87 (s, 1H), 7.84 (s, 1H), 7.78 (s, 1H), 7.54–7.52 (m, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.43–7.38 (m, 4H), 7.32–7.25 (m, 4H), 6.56 (m, 1H), 4.20 (m, 1H), 4.09 (m, 1H), 3.71–3.40 (m, 9H), 3.15 (brs, 1H), 3.03–2.91 (m, 2H), 2.87–2.77 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.6, 140.9, 139.3, 137.1, 135.5, 130.4, 129.7, 128.7, 128.0, 127.1, 126.9, 126.4, 121.2, 115.5, 113.1, 111.9, 103.2, 74.8, 74.7, 71.3, 70.6, 69.7, 39.4, 29.6 ppm. MS (ESI, m/z): 513 (M^+ + 1), 535 (M^+ + 23), HRMS (ESI): $C_{30}H_{32}N_4O_4$ calculated $[M + H]^+$ 513.2496, found 513.2495.

5.1.28. 6-(4-((S)-3-(2-((S)-3-(biphenyl-4-yl)-2-hydroxypropoxy) ethoxy)-2-hydroxypropyl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazol-2(3H)-one (**10**)

The procedure was the same as described above for the synthesis of **2**; the compound **10** was obtained as pale yellow solid (47.2 mg, 49% for 2 steps). $[\alpha]_{25}D$: 3.9 (c 0.47, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.59 (d, J = 1.8 Hz, 1H), 7.52–7.50 (m, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.40–7.36 (m, 3H), 7.31–7.25 (m, 4H), 7.07 (d, J = 8.6 Hz, 1H), 4.20 (m, 1H), 4.11 (m, 1H), 3.73–3.44 (m, 9H), 3.03–2.89 (m, 2H), 2.87–2.77 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 145.3, 140.7, 139.2, 137.1, 135.5, 132.5, 129.7, 128.7, 127.1, 126.9, 125.4, 120.6, 118.7, 114.7, 112.1, 74.8, 71.3, 70.6, 69.5, 39.4, 29.6 ppm. MS (ESI, m/z): 547 (M^+ + 1). HRMS (ESI): $C_{29}H_{30}N_4O_5S$ calculated $[M + H]^+$ 547.2010, found 547.2009.

5.1.29. (S)-1-(biphenyl-4-yl)-3-(2-((S)-2-hydroxy-3-(1-(4-phenoxybenzyl)-1H-1,2,3-triazol-4-yl)propoxy)ethoxy)propan-2-ol (**11**)

The procedure was the same as described above for the synthesis of **2**; the compound **11** was obtained as white solid (82.1 mg, 79% for 3 steps). $[\alpha]_{25}D$: 3.9 (c 0.56, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 7.3 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.40 (dd, J = 7.6 Hz, 2H), 7.36–7.25 (m, 6H), 7.18 (d, J = 8.5 Hz, 2H), 7.10 (dd, J = 7.4 Hz, 1H), 6.98 (d, J = 7.8 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 5.37 (s, 2H), 4.07 (m, 2H), 3.71 (brs, 1H), 3.64–3.35 (m, 9H), 2.92–2.75 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 156.6, 144.9, 140.9, 139.3, 137.3, 129.9, 129.8, 129.7, 129.4, 128.8, 127.1, 127.0, 123.8, 122.1, 119.3, 118.9, 74.9, 74.8, 71.2, 70.6, 69.6, 53.4, 39.5, 29.7 ppm. MS (ESI, m/z): 580 (M^+ + 1), 602 (M^+ + 23), HRMS (ESI): $C_{35}H_{37}N_3O_5$ calculated $[M + H]^+$ 580.2806, found 580.2810.

5.1.30. 4-((4-((S)-3-(2-((S)-3-(biphenyl-4-yl)-2-hydroxypropoxy) ethoxy)-2-hydroxypropyl)-1H-1,2,3-triazol-1-yl)methyl) benzonitrile (**12**)

The procedure was the same as described above for the synthesis of **2**; the compound **12** was obtained as white solid (83.4 mg, 81% for 2 steps). $[\alpha]_{25}D$: 5.9 (c 0.64, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 7.3 Hz, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.44–7.40 (m, 3H), 7.34–7.26 (m, 5H), 5.48 (s, 2H), 4.07 (m, 2H), 3.68–3.38 (m, 9H), 3.10 (brs, 1H), 2.95–2.79 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3, 140.9, 140.0, 139.4, 137.2, 132.8, 129.8, 128.8, 128.3, 127.2, 127.1, 126.9, 122.4, 118.1, 112.7, 74.8, 74.7, 71.2, 70.6, 69.5, 53.2, 39.4, 29.6 ppm. MS (ESI, m/z): 513 (M^+ + 1), 535 (M^+ + 23), HRMS (ESI): $C_{30}H_{32}N_4O_4$ calculated $[M + H]^+$ 513.2496, found 513.2494.

5.1.31. (S)-1-(biphenyl-4-yl)-3-(2-((S)-2-hydroxy-3-(1-(naphthalen-2-ylmethyl)-1H-1,2,3-triazol-4-yl)propoxy)ethoxy) propan-2-ol (**13**)

The procedure was the same as described above for the synthesis of **2**; the compound **13** was obtained as white solid (89.2 mg, 75% for 2 steps). $[\alpha]_{25}D$: 3.0 (c 0.74, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.79–7.77 (m, 2H), 7.67 (s, 1H), 7.54 (d, J = 7.2 Hz, 2H), 7.50–7.48 (m, 3H), 7.42–7.35 (m, 5H), 7.33–7.24 (m, 4H), 5.56 (s, 2H), 4.06 (m, 1H), 4.03 (m, 1H), 3.61 (m, 1H), 3.60–3.47 (m, 6H), 3.43–3.33 (m, 2H), 3.22 (brs, 1H), 2.87–2.75 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.0, 140.9, 139.2, 137.3, 133.2, 133.1, 132.2, 129.8, 129.0, 128.9, 128.8, 127.9, 127.8, 127.3, 127.1, 127.0, 126.7, 126.6, 125.3, 122.3, 74.8, 74.7, 71.2, 70.5, 69.5, 54.2, 39.4, 29.7 ppm. MS (ESI, m/z): 538 (M^+ + 1). HRMS (ESI): $C_{33}H_{35}N_3O_4$ calculated $[M + H]^+$ 538.2700, found 538.2700.

5.1.32. (S)-1-(1-(biphenyl-3-ylmethyl)-1H-1,2,3-triazol-4-yl)-3-(2-((S)-3-(biphenyl-4-yl)-2-hydroxypropoxy)ethoxy)propan-2-ol (**14**)

The procedure was the same as described above for the synthesis of **2**; the compound **14** was obtained as white solid (82.1 mg, 77% for 3 steps). $[\alpha]_{25}D$: 6.1 (c 0.59, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.56–7.48 (m, 7H), 7.44–7.38 (m, 7H), 7.33 (dd, J = 7.9 Hz, 2H), 7.27–7.24 (m, 2H), 7.18 (d, J = 7.6 Hz, 1H), 5.48 (s, 2H), 4.08 (m, 1H), 4.04 (m, 1H), 3.62–3.35 (m, 9H), 3.19 (brs, 1H), 2.92–2.75 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 142.2, 141.0, 140.3, 139.3, 137.3, 135.4, 129.8, 129.5, 128.9, 128.7, 127.7, 127.4, 127.1, 127.0, 126.8, 122.2, 74.8, 74.7, 71.2, 70.6, 69.6, 54.0, 39.5, 29.7 ppm. MS (ESI, m/z): 564 (M^+ + 1), 586 (M^+ + 23), HRMS (ESI): $C_{35}H_{37}N_3O_4$ calculated $[M + H]^+$ 564.2857, found 564.2857.

5.1.33. (S)-1-(biphenyl-4-yl)-3-(2-((S)-2-hydroxy-3-(1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)propoxy)ethoxy) propan-2-ol (**15**)

The procedure was the same as described above for the synthesis of **2**; the compound **15** was obtained as pale yellow solid (88.6 mg, 80% for 3 steps). $[\alpha]_{25}D$: 6.9 (c 0.45, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.59–7.54 (m, 5H), 7.51 (d, J = 7.4 Hz, 2H), 7.42 (dd, J = 7.4 Hz, 2H), 7.34–7.27 (m, 5H), 4.07 (br, 1H), 3.93 (br, 1H), 3.63–3.40 (m, 8H), 3.45–3.40 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8, 139.3, 138.4, 137.1, 129.7, 128.7, 128.3, 127.1, 126.9, 126.0, 125.1, 123.1, 74.7, 74.6, 71.2, 70.6, 70.5, 69.3, 53.7, 39.4, 29.4 ppm. MS (ESI, m/z): 556 (M^+ + 1). HRMS (ESI): $C_{30}H_{32}F_3N_3O_4$ calculated $[M + H]^+$ 556.2418, found 556.2419.

*5.1.34. (S)-1-(biphenyl-4-yl)-3-(2-((S)-2-hydroxy-3-(1H-1,2,3-triazol-4-yl)propoxy)ethoxy)propan-2-ol (**16**)*

Compound **29** (88.5 mg, 0.2 mmol), sodium ascorbate (15.8 mg, 0.08 mmol) $CuSO_4 \cdot 5H_2O$ (9.9 mg, 0.04 mmol), L-proline (13.8 mg, 0.12 mmol), Na_2CO_3 (12.7 mg, 0.12 mmol) and sodium azide (26.3 mg, 0.4 mmol) were suspended in DMSO/H_2O (2 mL, 4:1). The mixture was stirred overnight at 85 °C. Then water (8 mL) was added and the crude mixture was extracted with ethyl acetate (10 mL × 3), the combined organic layers were washed with brine, dried over Na_2SO_4 (anhydrous), filtered and concentrated to give a crude compound, which was used as such in the next step.

The crude product obtained above was then dissolved in a solution of THF and CH_3OH (1.2 mL, V/V, 1:2), added 6 N HCl (0.8 mL), stirred for 3 h at room temperature. The solution was quenched by saturated $NaHCO_3$ (3 mL) solution, extracted with ethyl acetate (10 mL × 3). Then the combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 (anhydrous), filtered and concentrated. Purification by silical gel chromatography afforded **16** as white solid (43.6 mg, 55% for 2 steps). $[\alpha]_{25}D$: 10.2 (*c* 0.32, CHCl3). ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 7.5 Hz, 2H), 7.50–7.48 (m, 3H), 7.41 (dd, J = 7.5 Hz, 2H), 7.33–7.25 (m, 3H), 4.10 (m, 2H), 3.66–3.38 (m, 8H), 2.86–2.75 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.8, 139.2, 137.1, 129.7, 128.7, 127.1, 126.9, 75.1, 75.0, 74.7, 71.2, 70.4, 69.2, 39.4, 29.7 ppm. MS (ESI, *m/z*): 398 ($M^+ + 1$). HRMS (ESI): $C_{22}H_{27}N_3O_4$ calculated $[M + H]^+$ 398.2074, found 398.2076.

*5.1.35. 2-(10-(4-((S)-3-(2-((S)-3-(biphenyl-4-yl)-2-hydroxypropoxy)ethoxy)-2-hydroxypropyl)-1H-1,2,3-triazol-1-yl)decyl)-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**17**)*

Compound **29** (88.5 mg, 0.2 mmol), appropriate quinones (1.2 equiv), sodium ascorbate (15.8 mg, 0.08 mmol), $CuSO_4 \cdot 5H_2O$ (9.9 mg, 0.04 mmol) and sodium azide (15.6 mg, 0.24 mmol) were dissolved in DMF/H_2O (2 mL 2:1). The mixture was stirred overnight at 85 °C. Then water (8 mL) was added and the crude mixture was extracted with ethyl acetate (10 mL × 3), the combined organic layers were washed with saturated NH_4Cl solution and brine, dried over Na_2SO_4 (anhydrous), filtered and concentrated to give a crude compound, which was used in the subsequent step.

The crude product obtained was then dissolved in a solution of *tert*-butanol, and then PPTS (502 mg, 2 mmol) was added, the mixture was stirred for 24 h under reflux. The solvent was removed; the mixture was diluted with CH_3Cl_3, washed with saturated aqueous NH_4Cl solution and brine. The organic phase was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The resulting mixture was purified by silica gel column chromatography to give **17** as a yellow solid (108 mg, 75% for 2 steps). $[\alpha]_{25}D$: 14.8 (c 0.14, CHCl3). ^1H NMR (400 MHz, $CDCl_3$): δ 7.58–7.51 (m, 4H), 7.44–7.38 (m, 3H), 7.34–7.28 (m, 3H), 4.27 (t, J = 7.2 Hz, 2H), 4.11–4.06 (m, 2H), 3.98 (s, 6H), 3.70–3.55 (m, 6H), 3.49–3.40 (m, 2H), 2.92–2.81 (m, 4H), 2.43 (t, J = 7.2 Hz, 2H), 2.00 (s, 3H), 1.87–1.84 (m, 2H), 1.38–1.24 (m, 14H) ppm. ^{13}C NMR(125 MHz, $CDCl_3$): δ 184.7, 184.1, 144.4, 144.3, 143.0, 140.9, 139.4, 138.7, 137.1, 129.7, 128.7, 127.2, 127.1, 127.0, 121.9, 74.8, 74.7, 71.3, 70.6, 69.7, 61.1, 50.2, 39.4, 30.2, 29.7, 29.5, 29.2, 28.9, 28.7, 26.5, 26.4, 11.9 ppm. MS (ESI, *m/z*): 718 ($M^+ + 1$), HRMS (ESI): $C_{41}H_{55}N_3O_8$ calculated $[M + H]^+$ 718.4062, found 718.4060.

*5.1.36. 2-(10-(4-((S)-3-(2-((S)-3-(biphenyl-4-yl)-2-hydroxypropoxy)ethoxy)-2-hydroxypropyl)-1H-1,2,3-triazol-1-yl)decyl)-5-methoxy-3,6-dimethylcyclohexa-2,5-diene-1,4-dione (**18**)*

The procedure was the same as described above for the synthesis of **17**; the compound **18** was obtained as yellow solid (70 mg, 50% for 2 steps). $[\alpha]_{25}D$: 12.3 (*c* 0.19, CHCl3). ^1H NMR (400 MHz, $CDCl_3$): δ 7.58–7.51 (m, 4H), 7.44–7.38 (m, 3H), 7.34–7.28 (m, 3H), 4.27 (t, J = 7.2 Hz, 2H), 4.11–4.06 (m, 2H), 3.96 (s, 3H), 3.70–3.55 (m, 6H), 3.49–3.40 (m, 2H), 2.92–2.81 (m, 4H), 2.44 (t, J = 7.2 Hz, 2H), 2.00 (s, 3H), 1.93 (s, 3H), 1.87–1.84 (m, 2H), 1.38–1.24 (m, 14H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.1, 184.0, 155.5, 144.7, 144.3, 140.9, 139.4, 138.6, 137.1, 129.7, 128.7, 128.6, 127.2, 127.1, 127.0, 121.9, 74.8, 74.7, 71.3, 70.6, 69.7, 60.8, 50.2, 39.4, 30.3, 29.9, 29.7, 29.6, 29.3, 28.9, 28.8, 26.7, 26.5, 11.7, 8.8 ppm. MS (ESI, *m/z*): 702 ($M^+ + 1$), HRMS (ESI): $C_{41}H_{55}N_3O_7$ calculated $[M + H]^+$ 702.4113, found 702.4113, $[M + Na]^+$ 724.3932, found 724.3933.

*5.1.37. 2-(10-(4-((S)-3-(2-((S)-3-(biphenyl-4-yl)-2-hydroxypropoxy)ethoxy)-2-hydroxypropyl)-1H-1,2,3-triazol-1-yl)decyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (**19**)*

The procedure was the same as described above for the synthesis of **17**; the compound **19** was obtained as yellow solid (80 mg, 58% for 2 steps). $[\alpha]_{25}D$: 10.4 (c 0.18, CHCl3). ^1H NMR (400 MHz, $CDCl_3$): δ 7.58–7.51 (m, 4H), 7.44–7.38 (m, 3H), 7.34–7.28 (m, 3H), 4.27 (t, J = 7.2 Hz, 2H), 4.11–4.06 (m, 2H), 3.70–3.55 (m, 6H), 3.49–3.40 (m, 2H), 2.92–2.81 (m, 4H), 2.44 (t, J = 7.2 Hz, 2H), 2.00 (s, 9H), 1.87–1.84 (m, 2H), 1.38–1.24 (m, 14H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.9, 187.2, 144.5, 144.3, 140.9, 140.4, 140.1, 139.4, 137.1, 129.7, 128.7, 127.2, 127.1, 127.0, 121.9, 74.8, 74.7, 71.3, 70.6, 69.7, 50.2, 39.4, 30.2, 29.8, 29.6, 29.4, 29.3, 28.9, 28.8, 26.6, 26.5, 12.3, 12.1 ppm. MS (ESI, *m/z*): 686 ($M^+ + 1$), HRMS (ESI): $C_{41}H_{55}N_3O_6$ calculated $[M + H]^+$ 686.4164, found 686.4163.

*5.1.38. 2-(10-(4-((S)-3-(2-((S)-3-(biphenyl-4-yl)-2-hydroxypropoxy)ethoxy)-2-hydroxypropyl)-1H-1,2,3-triazol-1-yl)decyl)-3-methylnaphthalene-1,4-dione (**20**)*

The procedure was the same as described above for the synthesis of **17**; the compound **20** was obtained as yellow solid (92 mg, 65% for 2 steps). $[\alpha]_{25}D$: 6 (c 0.12, CHCl3). ^1H NMR (400 MHz, $CDCl_3$): δ 8.08–8.06 (m, 2H), 7.69–7.67 (m, 2H), 7.58–7.51 (m, 4H), 7.44–7.38 (m, 3H), 7.34–7.28 (m, 3H), 4.27 (t, J = 7.2 Hz, 2H), 4.11–4.06 (m, 2H), 3.70–3.55 (m, 6H), 3.49–3.40 (m, 2H), 2.92–2.81 (m, 4H), 2.62 (t, J = 7.2 Hz, 2H), 2.18 (s, 3H), 1.87–1.84 (m, 2H), 1.48–1.27 (m, 14H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) : δ 185.4, 184.7, 147.5, 144.3, 143.1, 140.9, 139.3, 137.1, 133.3, 133.2, 132.2, 129.7, 128.7, 127.2, 127.1, 127.0, 126.2, 126.1, 121.9, 74.8, 74.7, 71.2, 70.6, 69.7, 50.2, 39.4, 30.2, 29.9, 29.6, 29.3, 28.9, 28.7, 27.1, 26.5, 12.6 ppm. MS (ESI, *m/z*): 708 ($M^+ + 1$), HRMS (ESI): $C_{43}H_{53}N_3O_6$ calculated $[M + H]^+$ 708.4007, found 708.4008.

*5.1.39. 2-(6-(4-((S)-3-(2-((S)-3-(biphenyl-4-yl)-2-hydroxypropoxy)ethoxy)-2-hydroxypropyl)-1H-1,2,3-triazol-1-yl)hexyl)-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**21**)*

The procedure was the same as described above for the synthesis of **17**; the compound **21** was obtained as yellow solid (82 mg, 62% for 2 steps). $[\alpha]_{25}D$: 12 (c 0.17, CHCl3). ^1H NMR (400 MHz, $CDCl_3$): δ 7.58–7.51 (m, 4H), 7.44–7.38 (m, 3H), 7.34–7.28 (m, 3H), 4.27 (t, J = 7.2 Hz, 2H), 4.11–4.06 (m, 2H), 3.98 (s, 6H), 3.70–3.55 (m, 6H), 3.49–3.40 (m, 2H), 2.92–2.81 (m, 4H), 2.42 (t, J = 7.2 Hz, 2H), 2.00 (s, 3H), 1.87–1.84 (m, 2H), 1.38–1.30 (m, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.5, 184.1, 144.4, 144.3, 142.6, 140.9, 139.3, 138.8, 137.1, 129.7, 128.7, 127.13, 127.10, 126.9, 121.9, 74.7, 74.6, 71.2, 70.6, 69.6, 61.1, 50.1, 39.4, 30.0, 29.5, 29.0, 28.3, 26.1, 11.9 ppm. MS (ESI, *m/z*): 662 ($M^+ + 1$), HRMS (ESI): $C_{37}H_{47}N_3O_8$ calculated $[M + H]^+$ 662.3436, found 662.3439.

*5.1.40. 2-(15-(4-((S)-3-(2-((S)-3-(biphenyl-4-yl)-2-hydroxypropoxy)ethoxy)-2-hydroxypropyl)-1H-1,2,3-triazol-1-yl)pentadecyl)-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**22**)*

The procedure was the same as described above for the synthesis of **17**; the compound **22** was obtained as yellow solid

(110 mg, 70% for 2 steps). $[\alpha]_{25}D$: 16.2 (c 0.17, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) : δ 7.58–7.51 (m, 4H), 7.44–7.38 (m, 3H), 7.34–7.28 (m, 3H), 4.27 (t, $J = 7.2$ Hz, 2H), 4.11–4.06 (m, 2H), 3.98 (s, 6H), 3.70–3.55 (m, 6H), 3.49–3.40 (m, 2H), 2.92–2.81 (m, 4H), 2.44 (t, $J = 7.2$ Hz, 2H), 2.00 (s, 3H), 1.87–1.84 (m, 2H), 1.77–1.75 (m, 2H), 1.38–1.24 (m, 24H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.7, 184.1, 144.3, 143.1, 140.9, 139.3, 138.6, 137.1, 129.7, 128.7, 127.2, 127.1, 127.0, 121.8, 74.8, 74.7, 71.2, 70.6, 70.5, 69.6, 61.1, 50.2, 39.4, 30.3, 29.8, 29.6, 29.5, 29.4, 29.4, 29.0, 28.7, 26.5, 26.4, 11.9 ppm. MS (ESI, m/z): 788 ($M^+ + 1$), HRMS (ESI): $C_{46}H_{65}N_3O_8$ calculated $[M + H]^+$ 788.4844, found 788.4846.

5.2. Biological assays

5.2.1. Cell culture conditions

Human gastric cancer cell lines (SGC7901) and normal human lung fibroblasts (HLF) were cultured in Dulbecco's Modified Eagle's Medium (DMEM), supplemented with penicillin-streptomycin, L-glutamine, and 10% FBS. Human colorectal carcinoma cell lines (HCT-116) were cultured in F12/DMEM, supplemented with penicillin-streptomycin, L-glutamine, and 10% FBS. All cell lines were maintained in a humidified atmosphere of 5% CO_2 at 37 °C.

5.2.2. Cell viability assay

Cells (5×10^3) were plated in flat-bottomed 96-well microplates. Background control wells lacking the cells but containing the same volume of media were included in each assay plate. 16 h after seeding, new media was added which contained increasing concentrations of tested compounds at 0.01–10 μM or vehicle control (DMSO). Cells were further incubated for 72 h and then treated with MTT (Sigma–Aldrich, 10 μl/well, 5 mg ml^{-1}) and incubated for another 4 h. Then the media was removed and 150 μl DMSO was added to each well including controls and blanks. After swirled gently, the absorbance in each well at 570 nm in a microtiter plate reader was measured with a reference wavelength at 690 nm. Experiments were performed at least in replicates of four, and growth inhibition rate was calculated: (%) = {1 − [ΔOD (compounds) − ΔOD (Blank)]/[ΔOD (controls) − ΔOD (Blank)]} × 100%. The growth inhibition (GIC_{50}) for each compound was defined as a concentration of drug leading to a 50% reduction in A570 compared with controls.

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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.2014.03.062.

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