Synthesis of a Novel Series of 1,2,3-Triazole-Containing Artemisinin Dimers with Potent Anticancer Activity Involving Huisgen 1,3-Dipolar Cycloaddition Reaction

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Abstract: A series of C-10 acetal triazolylartemisinin dimers were prepared via the Huisgen 1,3-dipolar cylcoaddition of artemisinin-derived terminal alkynes with 10α-azidoartemisinin and various aliphatic and aromatic diazides. All the artemisinin dimers synthesized exhibited strong growth inhibition activity against several cancer cell lines.

Key words: artemisinin, *Artemisia annua*, antimalarial, 1,2,3-triazole, artemisinin dimer

The importance of artemisinin[1] (**1**) and its derivatives, for example, artemether,[2] arteether,[2] sodium artesunate,[3] etc. as chemotherapeutic agents for the treatment of chloroquine resistant malaria needs no emphasis (Figure 1). Artemisinin is a sesquiterpene lactone endoperoxide isolated from the Chinese medicinal plant *Artemisia annua* L. This highly oxygenated sesquiterpene lactone peroxide,[4] unlike most other antimalarials, lacks nitrogen-containing heterocyclic ring systems and is found to be a superior plasmocidal and blood schizontocidal agent compared to conventional antimalarial drugs, such as chloroquine, quinine, etc. against malaria strains, without obvious adverse effects on patients.

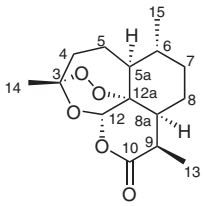

Figure 1 Structure of artemisinin (**1**)

In the mid 1990's selective cytotoxicity of artemisinin-derived peroxide towards cancer cells[5–10] also became known. The majority of derivatives of artemisinin prepared so far are through C-10, and the members through C-13 are relatively less.[5] Artemisinin dimers are a new class of artemisinin derivatives obtained by joining two artemisinin molecules without destroying their endoperoxide linkages.[5] This class of molecules have been reported to have much better antimalarial and anticancer activities than many of the monomers.[11–14] Since the pioneering work of Beekman et al., a small group of chemists have ventured into this field and synthesized several classes of artemisinin dimers[15] with varying degree of bioactivity, and quite a few of them are in different stages of development as drug candidates.

Artemisinin, being a very sensitive molecule, restricts wide-spread derivatization for library synthesis for further clinical development. So far majority of the derivatization of artemisinin were carried out on the C-10 acetal[5] and to a lesser extent on C-13 carbon[5] via artemisitene, a natural analogue of artemisinin, which also co-exists with artemisinin in *Artemisia annua*[1] and also can be synthesized from artemisinin via a selenoxide elimination route.[16] Several authors also have been able to hydroxylate unactivated carbons (C-4, C-5, C-6, and C-7) of the artemisinin molecule using microbial fermentation.[17–22] In continuation of our interest on derivatization of artemisinin for further value addition, we recently synthesized a series of artemisinin dimers involving dinitroaliphatics as the linkers.[23] In this communication, we wish to report the synthesis of a series of hitherto unknown artemisinin dimers having triazole moiety involving Huisgen 1,3-dipolar cycloaddition reaction.[24,25] It is worth emphasizing here that due to sensitive nature of the peroxide linkage, widespread use of stringent reaction conditions and reagents on artemisinin for its derivatization is difficult. We have been successfully able to apply Huisgen 1,3-dipolar cycloaddition condition to synthesize this series of dimers in good to excellent yields.

The ever increasing demand for novel medicinally active compounds and the laborious process of lead discovery and optimization have resulted in the continuous search for simple and efficient methods for generation of libraries for biological screening. The 'click chemistry' has emerged as a fast and efficient approach for the synthesis of novel compounds with desired functionality.[26–29] In this paper, we will showcase the applicability of the copper-mediated Huisgen 1,3-dipolar cycloaddition of azides and alkynes resulting in 1,2,3-triazoles, one of the most powerful click reactions to date, to synthesize artemisinin dimer.[30–32] Several members of the 1,2,3-triazole family have indeed shown interesting biological properties.[33] For the first time we introduced this highly effective coupling

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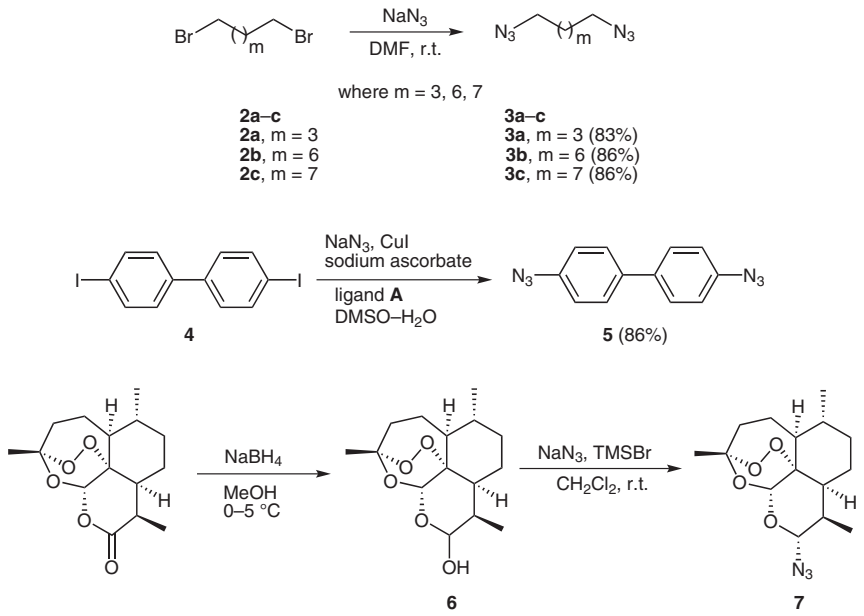
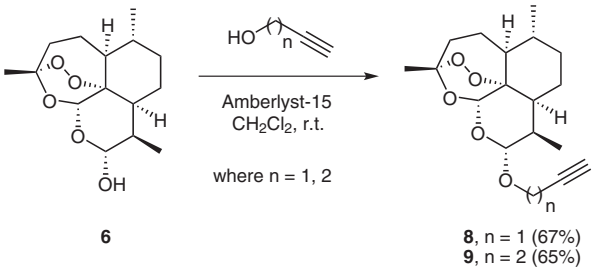


Scheme 1 Synthesis of aliphatic, aromatic diazides, and 10α-azidoartemisinin

method for the synthesis of artemisinin 1,2,4-trioxane dimers.[34]

Our synthetic strategy commences with the synthesis of diazido aliphatic[35] and aromatic[36] compounds from commercially available dihalides and also azido derivative of artemisinin itself (Scheme 1). Treatment of the dibromoaliphatic compound **2a–c** with sodium azide in dimethylformamide furnished the desired diazidoaliphatics **3a–c** in 80–86% isolated yields after 12 hours. Similarly, 4,4′-diiodobiphenyl (**4**) on treatment with sodium azide, cuprous iodide, sodium ascorbate, *N*,*N*′-dimethylethane-1,2-diamine (**A**) in dimethyl sulfoxide and water furnished the required 4,4′- diazidobiphenyl (**5**) in 86% isolated yield.[37] Artemisinin lactol **6** on treatment with sodium azide and bromotrimethylsilane in dichloromethane under inert atmosphere and at room temperature for 12 hours produced 10α-azidoartemisinin **7**.[24] We have synthesized artemisinin lactol from artemisinin by sodium borohydride reduction in methanol at low temperature.

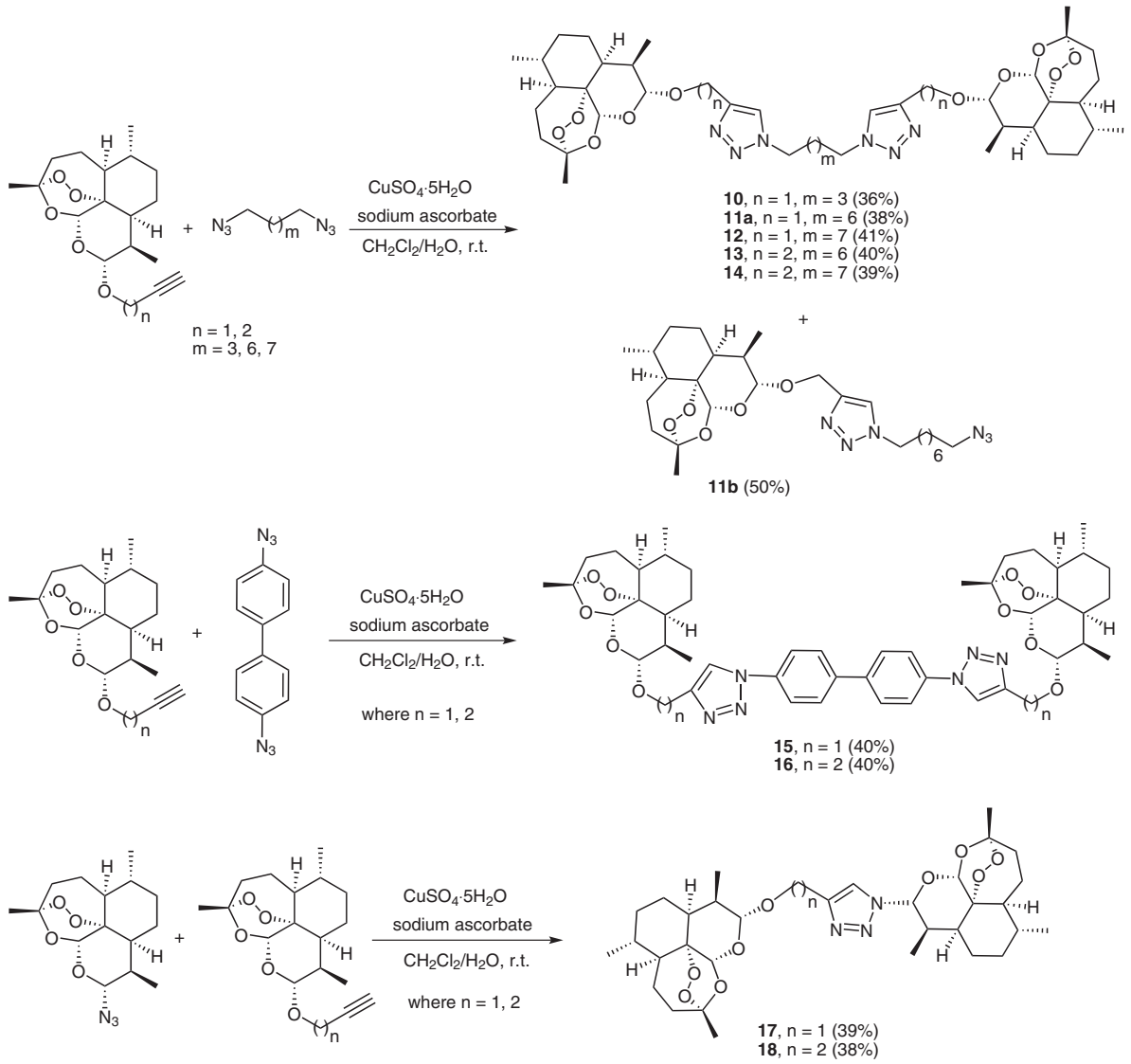
The alkyne precursor, viz. **8** and **9**, were synthesized from artemisinin lactol by treatment with propargyl alcohol and homopropargyl alcohol respectively in presence of Amberlyst-15 in anhydrous dichloromethane at room temperature (Scheme 2).



Scheme 2 Synthesis of terminal alkynes of artemisinin

Huisgen 1,3-dipolar cycloaddition[20] between the synthesized aliphatic and aromatic diazides and two alkyne derivatives of artemisinin **8** and **9** were carried out in the presence of copper sulfate and sodium ascorbate in dichloromethane and water at room temperature to furnish the desired artemisinin dimers **10** (36%), **11a** (38%), **12** (41%), **13** (40%), **14** (39%), **15** (40%), and **16** (40%) in isolated yield. In the case of **8** and 1,8-diazidooctane, one artemisinin monomer derivative **11b** (50%) could be isolated along with dimer **11a**. Reaction of 10α-azidoartemisinin with **8** and **9** produced artemisinin-derived 1,2,4-trioxane dimers **17** (39%) and **18** (38%) with a 1,2,3-triazole ring system. The stereochemistry of the C-10 centers of azidoartemisinin and two alkyne derivatives of artemisinin remained identical for each dimer. It was found that cycloaddition of artemisinin-derived terminal alkynes with various diazides catalyzed by Cu(I) can be conducted at room temperature leading exclusively to 4-substituted 1,2,3-triazoles (Scheme 3).

Nine novel artemisinin-derived triazole dimers and one artemisinin monomer were tested for in vitro anticancer activity against different human cancer cell lines using sulforhodamine B Assay. Some of the compounds showed encouraging results and these are summarized in Table 1. Compounds **15**, **16**, and **18** show 75%, 56%, and 66% growth inhibition against colon HCT-15 human cancer cell line. Compounds **14**, **11b**, **15**, and **18** are also promising exhibiting 60%, 64%, 64%, and 48% GI against lung cancer cell A-549 respectively. Among others, the compound **14** showed glimpses of superior activity (GI 71%) against human liver cancer cell line of HEP-2 type, which is comparable with that of mitomycin-c (GI 58% at 1×10^{-5} M concentration). On the other hand, compounds **14**, **11b**, **15**, **16**, and **18** showed 97%, 95%, 80%, 82%, and 79% growth inhibition respectively against leukemia THP-1 cell line, which are comparable with 5-fluorouracil



Scheme 3 General synthetic scheme for artemisinin-derived dimers containing triazole moieties

(GI 73% at 2×10^{-5} M concentration). Overall, compound **15** has shown good activity results against almost all three cancer cell lines (colon HCT-15, lung A-549 and leukemia THP-1) tested herein.

For the first time, we have synthesized a series of 1,2,3-triazole-containing artemisinin-derived 1,2,4-trioxane dimers using Husigen 1,3-dipolar cycloaddition reaction, which shows promising in vitro anticancer activity against several human cancer cell lines. Further study in this direction is in progress and will be reported in due course.

^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker DPX-300 NMR machine. IR spectra were recorded on a Perkin-Elmer 1640 FT-IR spectrometer. Optical rotations were measured on a Perkin-Elmer 343 polarimeter. Mass spectra were recorded on Waters Micro-mass ZQ 4000 (ESI Probe) spectrometer. Melting points are uncorrected and recorded on Büchi B-540 melting point apparatus. Column chromatography was performed with Merck silica gel (100–200 mesh) and preparative TLC was carried out on plates prepared with Merck Silica Gel G. Moisture sensitive reactions were conducted under a dry N_2 atmosphere. THF was distilled from benzophenone ketyl prior to use. All solvents were distilled at their boiling point and other commercially available reagents were used as received, unless otherwise stated.

Diazides 3a–c; General Procedure

In a 50 mL round-bottomed flask, sodium azide (6.98 mmol) was taken in DMF (5 mL), kept stirring for 10 min. Dibromoalkane (3.49 mmol) was added to the system and allowed to stir for 5 h. After completion of the reaction (as monitored by TLC, eluent: hexane), H_2O (30 mL) was added to the mixture. The mixture was extracted with Et_2O (3×30 mL) and the aqueous layer was extracted with EtOAc (3×30 mL). Both the organic parts were mixed, dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by column chromatography (hexane) to afford **3a–c** as colorless liquids.

3a

Yield: 83%; colorless liquid.

IR ($CHCl_3$): 2939, 2094, 1638, 1454 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.32$ (t, $J = 6.6$ Hz, 4 H, $N_3CH_2CH_2$), 1.63 (m, 4 H, aliphatic chain), 1.43 (m, 2 H, aliphatic chain).

Table 1 Proliferation Inhibition Assay Against Different Human Cancer Cell Lines[a]

Compound	Conc (M)	% Growth inhibition			
		Colon HCT-15	Lung A-549	Leukemia THP-1	Liver HEP-2
13	5×10^{-5}	25	32	68	39
14	5×10^{-5}	51	60	97	71
11b	5×10^{-5}	49	64	95	54
15	5×10^{-5}	78	64	80	–
16	5×10^{-5}	66	46	82	–
17	5×10^{-5}	63	22	62	–
18	5×10^{-5}	70	48	79	–
artemisinin	5×10^{-5}	31	29	–	–
artemisinin	1×10^{-5}	29	19	–	–
5-fluorouracil	2×10^{-5}	65	–	73	–
mitomycin-c	1×10^{-5}	–	–	–	58
15	1×10^{-5}	75	56	75	–
16	1×10^{-5}	56	41	63	–
18	1×10^{-5}	66	29	78	–

[a] No entries (–) are shown for compounds that were not tested against the indicated cell lines.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.1, 50.8, 28.3, 28.1, 23.5.

MS (ESI): *m*/*z* = 154 (M^+).

Anal. Calcd for $C_5H_{10}N_6$: C, 38.95; H, 6.54; N, 54.51. Found: C, 38.91; H, 6.49; N, 54.48.

3b

Yield: 86%; colorless liquid.

IR ($CHCl_3$): 2934, 2858, 2097, 1464, 1257 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.28 (t, *J* = 6.9 Hz, 4 H, $N_3CH_2CH_2$), 1.60 (m, 4 H, aliphatic chain), 1.34 (s, 8 H, aliphatic chain).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.3, 28.9, 28.7, 26.7, 26.5.

MS (ESI): *m*/*z* = 196 (M^+).

Anal. Calcd for $C_8H_{16}N_6$: C, 48.96; H, 8.22; N, 42.82. Found: C, 48.81; H, 8.11; N, 42.75.

3c

Yield: 86%; colorless liquid.

IR ($CHCl_3$): 2932, 2857, 2096, 1465, 1258 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.28 (t, *J* = 6.9 Hz, 4 H, $N_3CH_2CH_2$), 1.59 (m, 4 H, aliphatic chain), 1.32 (s, 10 H, aliphatic chain).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.3, 29.2, 29.0, 28.7, 26.8.

MS (ESI): *m*/*z* = 209.3 (M^+).

Anal. Calcd for $C_9H_{18}N_6$: C, 51.41; H, 8.63; N, 39.97. Found: C, 51.35; H, 8.57; N, 39.91.

4,4′-Diazidobiphenyl (5)

4,4′-Diiodobiphenyl (**4**; 199 mg, 0.492 mmol), NaN_3 (66 mg, 1.03 mmol), sodium ascorbate (4 mg, 0.0246 mmol), CuI (9.3 mg, 0.0492 mmol), ligand *N*,*N*′-dimethylethane-1,2-diamine (6.5 mg, 0.0738 mmol), and DMSO–H_2O (0.984 mL, 5:1) were introduced into a 50 mL two-necked round-bottomed flask equipped with a stirring bar. After degassing, argon was introduced and the reaction mixture was stirred at r.t. The progress of the reaction was followed by TLC (eluent: 20% EtOAc in hexane). After completion of the reaction, the crude reaction mixture was taken up in a mixture of brine (20 mL) and EtOAc (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (1% EtOAc in hexane) to afford **5** (99 mg, 86%); yellow solid; mp 121.8 °C.

IR ($CHCl_3$): 2924, 2102, 1495, 1299 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 4.6 Hz, 4 H, protons near N_3), 7.11 (d, *J* = 2 Hz, 4 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.2, 136.8, 128.1, 119.5.

MS (ESI): *m*/*z* = 260 (M^+ + Na).

Anal. Calcd for $C_{12}H_8N_6$: C, 61.01; H, 3.41; N, 35.58. Found: C, 61.10; H, 3.37; N, 35.52.

Azide 7

This compound was prepared according to the literature procedure.[24]

Alkyne Precursors 8 and 9; General Procedure

Compound **6** (3.54 mmol) and the appropriate acetylenic alcohol (3.54 mmol) were dissolved in anhyd CH_2Cl_2 (10 mL) and 800 mg Amberlyst-15 was added to the same under N_2 and stirred overnight. The reaction was monitored by TLC (eluent: 33% EtOAc in hexane). After completion of the reaction, the CH_2Cl_2 was filtered out, dried (Na_2SO_4), and concentrated under reduced pressure. The crude mixture was purified by column chromatography (5% EtOAc in hexane) to afford **8** and **9**.

8

Yield: 67%; white solid; mp 116.2 °C; $[\alpha]_D^{20}$ +259 (*c* 2.5, $CHCl_3$).

IR ($CHCl_3$): 3284, 2953, 2922, 2873, 1638, 1100, 1027 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.42 (s, 1 H, H-12), 4.99 (d, *J* = 3.42 Hz, 1 H, H-10), 4.32 (s, 2 H, C*H*$_2$C≡CH), 2.67 (m, 1 H, C≡CH), 2.4–1.51 (m, 12 H, arte. aliphatic), 1.44 (s, 3 H, 3-CH_3), 0.96 (d, *J* = 5.58 Hz, 3 H, 9-CH_3), 0.94 (d, *J* = 7.17 Hz, 3 H, 6-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 104.1, 100.6, 88.0, 81.0, 79.7, 73.9, 54.9, 52.5, 44.3, 37.4, 36.3, 34.5, 30.5, 26.1, 24.6, 24.4, 20.3, 12.8.

MS (ESI): *m*/*z* = 345 (M^+ + Na).

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.17; H, 8.01.

9

Yield: 65%; white solid; mp 105.8 °C; $[\alpha]_D^{20}$ +213 (*c* 2.5, $CHCl_3$).

IR ($CHCl_3$): 3287, 2939, 2922, 1646, 1104, 1026 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.47 (s, 1 H, H-12), 4.84 (d, *J* = 3.3 Hz, 1 H, H-10), 3.95 (m, 2 H, C*H*$_2$CH$_2$C≡CH), 3.59 (m, 2 H, CH$_2$C*H*$_2$C≡CH), 2.65 (m, 1 H, C≡CH), 2.49–1.48 (m, 12 H, arte. aliphatic), 1.44 (s, 3 H, 3-CH_3), 0.96 (d, *J* = 6.15 Hz, 3 H, 9-CH_3), 0.93 (d, *J* = 7.41 Hz, 3 H, 6-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 104.0, 101.9, 88.0, 81.1, 69.0, 66.2, 52.5, 44.4, 37.4, 36.4, 34.6, 34.4, 30.8, 26.1, 24.6, 24.3, 20.4, 20.0, 12.9.

MS (ESI): *m*/*z* = 358.9 (M^+ + Na).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 66.91; H, 8.27.

1,2,3-Triazole-Containing Artemisinin Dimers; General Procedure

Synthetic aliphatic and aromatic diazide (0.476 mmol) and artemisinin-derived alkyne (0.523 mmol) were taken in CH_2Cl_2 and H_2O (3 mL, 1:1) system in a 50 mL round-bottomed flask and stirred for 5 min. $CuSO_4 \cdot 5H_2O$ (1.15 mmol) and sodium ascorbate (1.46 mmol) were added and the reaction mixture was stirred at r.t. for 12 h. The progress of the reaction was monitored by TLC (eluent: EtOAc). After completion of the reaction, the crude mixture was partitioned between H_2O (15 mL) and CH_2Cl_2 (20 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by preparative TLC (EtOAc).

10

Yield: 36%; colorless gum; $[\alpha]_D^{20}$ +45.14 (*c* 2.05, $CHCl_3$).

IR ($CHCl_3$): 2924, 1453 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.54 (s, 1 H, triazole), 7.44 (s, 1 H, triazole), 5.42 (s, 1 H, H-12), 4.93 (d, *J* = 15.6 Hz, 1 H, H-10), 4.89 (s, 1 H, H-12′), 4.68 (d, *J* = 12.6 Hz, 1 H, H-10′), 4.35 (m, 4 H, OCH_2), 2.64–1.70 (m, 24 H, arte. aliphatic), 1.45 (s, 6 H, 3-CH_3, 3′-CH_3), 1.25 (s, 10 H, aliphatic chain), 0.95 (d, *J* = 6 Hz, 6 H, 9-CH_3, 9′-CH_3), 0.88 (d, *J* = 7.3 Hz, 6 H, 6-CH_3, 6′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.1, 145.0, 122.4, 121.8, 104.1, 101.4, 87.9, 81.1, 77.2, 61.4, 56.2, 56.0, 52.4, 49.7, 49.6, 44.3, 41.0, 37.3, 36.3, 34.5, 30.7, 30.3, 29.6, 29.3, 29.2, 28.7, 26.1, 24.6, 24.4, 22.9, 20.5, 20.3, 12.9.

MS (ESI): *m*/*z* = 762.2 (M^+ – 60 + Na).

Anal. Calcd for $C_{41}H_{62}N_6O_{10}$: C, 61.63; H, 7.82; N, 10.52. Found: C, 61.61; H, 7.78; N, 10.48.

11a

Yield: 38%; colorless gum; $[\alpha]_D^{20}$ +16.61 (*c* 0.55, $CHCl_3$).

IR ($CHCl_3$): 2923, 2850 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.53 (s, 1 H, triazole), 7.48 (s, 1 H, triazole), 5.42 (s, 1 H, H-12), 4.94 (d, *J* = 15.1 Hz, 1 H, H-10), 4.9 (s, 1 H, H-12′), 4.7 (d, *J* = 12.5 Hz, 1 H, H-10′), 4.37 (t, *J* = 6.9 Hz, 4 H, OCH_2), 2.6 (m, 4 H, aliphatic chain), 2.37–1.49 (m, 24 H, arte. aliphatic), 1.3 (s, 6 H, 3-CH_3, 3′-CH_3), 1.25 (s, 12 H, aliphatic), 0.94 (d, *J* = 6 Hz, 6 H, 9-CH_3, 9′-CH_3), 0.88 (d, *J* = 7.3 Hz, 6 H, 6-CH_3, 6′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.4, 145.4, 121.4, 121.3, 107.9, 102.0, 100.0, 93.6, 88.2, 84.0, 80.4, 68.6, 67.4, 67.1, 61.5, 55.5, 50.2, 50.1, 50.0, 46.7, 42.3, 35.7, 34.7, 33.2, 30.6, 30.2, 30.1, 29.0, 28.7, 28.6, 27.6, 26.5, 26.4, 26.3, 24.6, 21.6, 21.0, 20.5, 18.8, 12.4.

MS (ESI): *m*/*z* = 841 (M^+).

Anal. Calcd for $C_{44}H_{68}N_6O_{10}$: C, 62.82; H, 8.15; N, 9.99. Found: C, 62.45; H, 8.21; N, 9.89.

11b

Yield: 50%; colorless gum; $[\alpha]_D^{20}$ +72.28 (*c* 2.35, $CHCl_3$).

IR ($CHCl_3$): 2923, 2852, 2095 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1 H, triazole), 5.42 (s, 1 H, H-12), 4.95 (d, *J* = 9.51 Hz, 1 H, H-10), 4.91 (s, 2 H, OCH_2), 4.34 (t, *J* = 7.1 Hz, 2 H, CH_2 triazole end), 3.28 (t, *J* = 6.8 Hz, 2 H, CH_2N_3), 2.64 (m, 1 H, H-9), 2.3 (td, *J* = 3.9 Hz, 2 H, H-4), 2.05–1.56 (m, 9 H, arte. aliphatic), 1.45 (s, 3 H, 3-CH_3), 1.33 (s, 12 H, aliphatic chain), 0.94 (d, *J* = 6 Hz, 3 H, 9-CH_3), 0.89 (d, *J* = 7.3 Hz, 3 H, 6-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.9, 122.2, 104.1, 101.5, 87.9, 81.1, 61.6, 52.5, 51.3, 50.1, 44.3, 37.3, 36.4, 34.5, 30.8, 30.2, 28.9, 28.8, 28.7, 26.5, 26.3, 26.1, 24.6, 24.4, 20.3, 12.9.

MS (ESI): *m*/*z* = 518 (M^+).

Anal. Calcd for $C_{26}H_{42}N_6O_5$: C, 60.21; H, 8.12; N, 16.2. Found: C, 60.11; H, 8.41; N,16.01.

12

Yield: 41%; colorless gum; $[\alpha]_D^{20}$ +9.2 (*c* 1.5, $CHCl_3$).

IR ($CHCl_3$): 2922, 2851, 1219 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.54 (s, 1 H, triazole), 7.48 (s, 1 H, triazole), 5.26 (s, 1 H, H-12), 4.94 (d, *J* = 8.5 Hz, 1 H, H-10), 4.88 (s, 1 H, H-12′), 4.66 (d, *J* = 12.6 Hz, 1 H, H-10′), 4.36 (t, *J* = 7.1 Hz, 4 H, OCH_2), 3.57 (m, 2 H, H-9, H-9′), 2.45 (m, 4 H, H-4, H-4′), 2.17–1.66 (m, 18 H, arte. aliphatic), 1.55 (s, 6 H, 3-CH_3, 3′-CH_3), 1.28 (s, 18 H, aliphatic chain), 0.92 (d, *J* = 7.6 Hz, 6 H, 9-CH_3, 9′-CH_3, 0.87 (d, *J* = 6.3 Hz, 6 H, 6-CH_3, 6′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.7, 145.0, 122.2, 121.6, 108.0, 99.0, 93.7, 84.1, 77.4, 77.2, 69.48, 61.6, 56.3, 50.3, 50.2, 42.3, 40.5, 34.8, 34.6, 30.3, 30.1, 29.6, 29.0, 28.6, 26.2, 26.0, 24.9, 21.0, 18.8, 12.3.

MS (ESI): *m*/*z* = 855 (M^+).

Anal. Calcd for $C_{45}H_{70}N_6O_{10}$: C, 63.21; H, 8.25; N, 9.83. Found: C, 63.31; H, 8.20; N, 9.81.

13

Yield: 40%; colorless gum; $[\alpha]_D^{20}$ +15.7 (*c* 1.15, $CHCl_3$).

IR ($CHCl_3$): 2926, 2867, 1453, 1220 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1 H, triazole), 7.31 (s, 1 H, triazole), 6.2 (s, 1 H, H-12), 5.1 (s, 1 H, H-12′), 4.77 (d, *J* = 4.2 Hz, 1 H, H-10), 4.75 (d, *J* = 4.2 Hz, 1 H, H-10′), 4.32 (t, *J* = 7.17 Hz, 4 H, aliphatic chain), 3.9 (m, 4 H, C*H*$_2$CH$_2$), 3.59 (m, 2 H, H-9, H-9′), 2.9 (m, 4 H, OCH$_2$C*H*$_2$), 2.4–1.6 (m, 22 H, arte. aliphatic), 1.55 (s, 6 H, 3-CH_3, 3′-CH_3), 1.3 (s, 12 H, aliphatic), 0.91 (d, *J* = 3.6 Hz, 6 H, 9-CH_3, 9′-CH_3), 0.86 (d, *J* = 2.8 Hz, 6 H, 6-CH_3, 6′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 147, 146, 121.3, 107.9, 100.0, 93.6, 88.3, 84.0, 80.4, 69.5, 67.5, 55.5, 50.1, 46.8, 42.4, 40.5, 35.8, 34.7, 33.2, 30.6, 30.3, 29.6, 28.7, 26.3, 24.9, 24.6, 21.6, 21.0, 20.5, 18.8, 12.4.

MS (ESI): *m*/*z* = 809 (M^+ – 60).

Anal. Calcd for $C_{46}H_{72}N_6O_{10}$: C, 63.57; H, 8.35; N, 9.67. Found: C, 63.42; H, 8.31; N, 9.59.

14

Yield: 39%; colorless gum; $[\alpha]_D^{20}$ +18.6 (*c* 2.0, $CHCl_3$).

IR ($CHCl_3$): 2926, 2870, 1220 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1 H, triazole), 7.32 (s, 1 H, triazole), 6.02 (s, 1 H, H-12), 5.1 (s, 1 H, H-12′), 4.77 (d, *J* = 4.3 Hz, 1 H, H-10), 4.74 (d, *J* = 4.19 Hz, 1 H, H-10′), 4.29 (t, *J* = 7 Hz, 4 H, aliphatic chain), 3.56 (m, 2 H, H-9, H-9′), 3.02 (m, 4 H, OCH_2CH$_2$), 2.5–1.64 (m, 22 H, arte. aliphatic), 1.55 (s, 6 H, 3-CH_3, 3′-CH_3), 1.29 (s, 18 H, aliphatic chain), 0.94 (d, *J* = 6.1 Hz, 6 H, 9-CH_3, 9′-CH_3), 0.87 (d, *J* = 4.02 Hz, 6 H, 6-CH_3, 6′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.4, 145.5, 145.3, 121.2, 107.9, 102.0, 100.0, 93.6, 88.3, 84.0, 80.4, 69.4, 68.6, 67.5, 67.2, 55.5, 50.1, 50.0, 46.7, 42.4, 40.5, 35.7, 34.7, 33.2, 30.6, 30.3, 29.1, 28.9, 27.7, 26.5, 26.4, 24.9, 24.6, 21.6, 21.0, 20.5, 18.8, 12.46, 12.41.

MS (ESI): *m*/*z* = 883.7 (M^+).

Anal. Calcd for $C_{47}H_{74}N_6O_{10}$: C, 63.92; H, 8.45; N, 9.52. Found: C, 63.91; H, 8.38; N, 9.48.

15

Yield: 40%; colorless gum; $[\alpha]_D^{20}$ +29.5 (*c* 3.1, $CHCl_3$).

IR ($CHCl_3$): 2921, 2845, 1219 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (s, 1 H, triazole), 8.0 (s, 1 H, triazole), 7.89 (m, 4 H_{arom}), 7.80 (m, 4 H_{arom}), 5.47 (s, 1 H, H-12), 5.34 (s, 1 H, H-12′), 5.06 (d, *J* = 4.6 Hz, 1 H, H-10), 5.0 (s, 2 H, OCH_2), 4.97 (d, *J* = 4.3 Hz, 1 H, H-10′), 4.77 (s, 2 H, OCH_2′), 3.59 (m, 2 H, H-9, H-9′), 2.38 (td, 4 H, H-4, H-4′), 2.17–1.47 (m, 18 H, arte. aliphatic), 1.25 (s, 6 H, 3-CH_3, 3′-CH_3), 0.93 (d, *J* = 2.7 Hz, 6 H, 9-CH_3, 9′-CH_3), 0.89 (d, *J* = 3.1 Hz, 6 H, 6-CH_3, 6′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.99, 145.9, 140.0, 136.6, 128.3, 120.9, 120.7, 120.5, 108.0, 104.2, 101.8, 99.4, 93.8, 88.0, 84.1, 81.1, 77.2, 69.5, 61.5, 52.4, 44.3, 42.4, 40.6, 37.3, 36.3, 34.8, 34.6, 34.5, 30.8, 30.3, 29.7, 26.1, 25.0, 24.6, 24.4, 21.0, 20.3, 18.8, 13.0, 12.3.

MS (ESI): *m*/*z* = 881 (M^+).

Anal. Calcd for $C_{48}H_{60}N_6O_{10}$: C, 65.44; H, 6.86; N, 9.54. Found: C, 65.35; H, 6.81; N, 9.45.

16

Yield: 40%; colorless gum; $[\alpha]_D^{20}$ +33.3 (*c* 2.3, $CHCl_3$).

IR ($CHCl_3$): 2924, 2873, 1508, 1021 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (s, 1 H, triazole), 7.88 (s, 1 H, triazole), 7.86 (m, 4 H_{arom}), 7.78 (m, 4 H_{arom}), 5.26 (s, 1 H, H-12), 5.18 (s, 1 H, H-12′), 4.86 (d, *J* = 3.3 Hz, 1 H, H-10), 4.82 (d, *J* = 4.1 Hz, 1 H, H-10′), 3.75 (m, 4 H, OCH_2CH$_2$), 3.57 (m, 2 H, H-9, H-9′), 3.13 (m, 4 H, OCH_2CH_2), 2.21–1.63 (m, 22 H, arte. aliphatic), 1.43 (s, 6 H, 3-CH_3, 3′-CH_3), 0.90 (d, *J* = 7.9 Hz, 6 H, 9-CH_3, 9′-CH_3), 0.80 (d, *J* = 6.3 Hz, 6 H, 6-CH_3, 6′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.4, 139.8, 136.7, 128.3, 128.2, 120.6, 119.5, 107.9, 104.0, 101.8, 100.1, 93.5, 87.8, 84.0, 81.0, 77.2, 69.5, 67.1, 67.0, 52.4, 44.2, 42.4, 40.5, 37.3, 36.3, 34.7, 34.5, 30.8, 30.3, 30.2, 29.6, 26.5, 26.1, 24.9, 24.6, 24.3, 21.0, 20.2, 18.8, 13.0, 12.4.

MS (ESI): *m*/*z* = 909 (M^+).

Anal. Calcd for $C_{50}H_{64}N_6O_{10}$: C, 66.06; H, 7.10; N, 9.24. Found: C, 66.12; H, 7.04; N, 9.21.

Compounds 17 and 18; General Procedure

Artemisinin-derived alkyne (0.645 mmol) and azido derivative of artemisinin (0.645 mmol) were taken in CH_2Cl_2 and H_2O (3 mL, 1:1) system in a 50 mL round-bottomed flask and allowed to stir. $CuSO_4{\cdot}5H_2O$ (0.709 mmol) and sodium ascorbate (1.80 mmol) were added to the mixture and stirring was continued at r.t. The progress of the reaction was monitored by TLC (eluent: EtOAc). After completion of the reaction, H_2O (15 mL) was added and the crude reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by TLC (EtOAc) to afford **17** and **18**.

17

Yield: 39%; colorless gum; $[\alpha]_D^{20}$ –13.5 (*c* 1.8, $CHCl_3$).

IR ($CHCl_3$): 2924, 1453 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.7 (s, 1 H, triazole), 5.86 (d, *J* = 10.7 Hz, 1 H, H-10), 5.45 (s, 1 H, H-12), 5.27 (s, 1 H, H-12′), 4.90 (d, *J* = 4.2 Hz, 1 H, H-10′), 4.89 (s, 2 H, OCH_2), 3.59 (m, 2 H, H-9, H-9′), 2.87–1.25 (m, 22 H, arte aliphatic), 0.93 (s, 3 H, 3-CH_3), 0.908 (s, 3 H, 3′-CH_3), 0.86 (d, *J* = 6.3 Hz, 6 H, 9-CH_3, 9′-CH_3), 0.79 (d, *J* = 7 Hz, 6 H, 6-CH_3, 6′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.7, 119.9, 109.0, 108.0, 104.8, 99.7, 95.9, 86.7, 84.1, 83.4, 79.8, 69.5, 69.1, 61.7, 51.4, 42.5, 41.6, 37.3, 34.8, 34.7, 33.9, 32.0, 29.6, 29.3, 25.7, 25.0, 24.5, 22.3, 21.0, 18.8, 18.6, 12.4, 12.2.

MS (ESI): *m*/*z* = 631 (M^+).

Anal. Calcd for $C_{33}H_{49}N_3O_9$: C, 62.74; H, 7.82; N, 6.65. Found: C, 62.71; H, 7.79; N, 6.60.

18

Yield: 38%; colorless gum; $[\alpha]_D^{20}$ –10.8 (*c* 1.7, $CHCl_3$).

IR ($CHCl_3$): 2925, 1454 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 1 H, triazole), 5.83 (d, *J* = 10.2 Hz, 1 H, H-10), 5.44 (s, 1 H, H-12), 5.22 (s, 1 H, H-12′), 4.77 (d, *J* = 4.1 Hz, 1 H, H-10′), 4.1 (m, 2 H, OCH_2CH$_2$), 3.6 (m, 2 H, H-9, H-9′), 2.99 (m, 2 H, OCH_2CH_2), 2.85–1.25 (m, 22 H, arte. aliphatic), 0.94 (s, 3 H, 3-CH_3), 0.92 (s, 3 H, 3′-CH_3), 0.88 (d, *J* = 2.7 Hz, 6 H, 9-CH_3, 9′-CH_3), 0.86 (d, *J* = 7 Hz, 6 H, 6-CH_3, 6′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.4, 145.5, 121.4, 121.3, 102, 88.3, 80.4, 77.2, 68.6, 67.2, 61.6, 55.6, 50.1, 50, 46.8, 35.8, 33.2, 30.6, 30.2, 30.1, 29.7, 28.6, 27.7, 26.4, 26.2, 24.6, 21.6, 20.5, 12.4.

MS (ESI): *m*/*z* = 668 (M^+ + Na).

Anal. Calcd for $C_{34}H_{51}N_3O_9$: C, 63.24; H, 7.96; N, 6.51. Found: C, 63.21; H, 7.89; N, 6.49.

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