Synthesis and Anticancer Activity of Novel Deoxoartemisinin–Glycolipid Hybrids

Dongguk Min,[a,#] Minkyu Kim,[a,#] Jérémy Ricci,[a] Sora Jung,[a] Kirim Kim,[b] Won-Yoon Chung,[b] Kwang-Kyun Park,[b] and Mankil Jung*[,a]

[a] *Department of Chemistry, Yonsei University; Seoul 120–749, Korea: and* [b] *Department of Oral Biology, College of Dentistry, Yonsei University; Seoul 120–752, Korea.*

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The practical synthesis and anticancer activity of novel deoxoartemisinin–glycolipid hybrids, which incorporate two drugs into a single molecule and can impact multiple targets simultaneously are presented. These hybrids exhibited potent *in vitro* anticancer activity against several human cancer cell lines. The deoxoartemisinin–glycolipid hybrids generally demonstrated better anticancer activity than either artemisinin or daumone alone and cisplatin.

Key words anticancer activity; oral squamous carcinoma; deoxoartemisinin; glycolipid hybrid

Daumone (**1**) (Fig. 1), a life expanding glycolipid isolated from *Caenorhabditis elegans*, was identified for the first time by our laboratory as a dauer-inducing pheromone, and its total synthesis was presented.[1)] While some previous studies have presented glycolipid derivatives with anticancer activity, the relatively weak activity for this compound class has generally discouraged its use for anticancer chemotherapeutic agents.[2–6)] However, glycosphingolipids found in a specific class of invertebrate that do not have sialic acids suppressed melanoma cell proliferation.[7)] Furthermore, glycolipids isolated from spinach have been shown to inhibit DNA polymerase activity and mitochondrial pol replication.[8)] Recently, we reported the synthesis of novel glycolipid derivatives through stereospecific α-glycosylation to afford di- and tri-rhamnoside daumone derivatives.[9)] Most of the derivatives possessed potent anticancer activity against human cancer cell lines with an effective concentration in the nanomolar range, comparable to doxorubicin.[9)]

Artemisinin (**2**) (Fig. 1), also known as *qinghaosu*, a natural tetracyclic sesquiterpene trioxane isolated from *Artemisia annua* L.,[10)] and its derivatives have been used clinically to treat drug-resistant malaria.[11–15)] In addition to their well-known antimalarial activity, artemisinin and its derivatives also possess potent antiangiogenic activity,[16–23)] and several research groups have demonstrated potential antitumor properties for this compound class.[20,24–31)] We have shown that non-acetal 12β(C–C)-type amide derivatives of deoxoartemisinin exhibit higher *in vitro* anticancer activity[22)] along with 20 times greater acid stability than acetal (C–O)-type derivatives of artemisinin.[32)]

One approach that has been developed to improve anticancer activity is the use of hybrid drugs, which incorporate two drugs into a single molecule[33)] and can impact multiple targets simultaneously. Since cancer is a complex disease, it is unlikely that a single functional targeted drug will be effective for treating this most advanced disease. Combined drugs that impact multiple targets simultaneously are better at controlling complex disease systems, are less prone to drug resistance.[33)] We recently reported that non-acetal 12β(C–C)-type artemisinin–glycolipid hybrids show strong antiangiogenic activity,[22)] with twice the potency of the known antiangiogenic agents fumagillin and thalidomide.[22)]

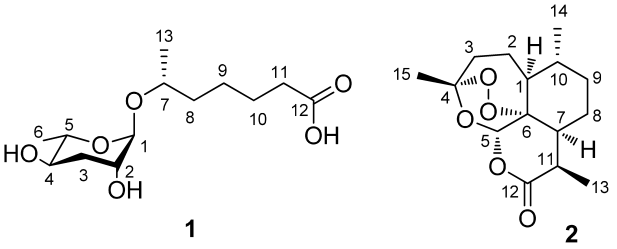

Fig. 1. Structure of Daumone (**1**) and Artemisinin (**2**)

These promising results encouraged us to further prepare a series of 12β(C–C)-type deoxoartemisinin–glycolipid hybrids and to test them as anticancer agents. Although gefitinib has been reported to be cytotoxic against an oral cancer cell line,[34)] no other anti-oral cancer agent has been reported in the literature to date. In this study we report the practical synthesis and exceptional *in vitro* anti-oral and anti-lung cancer activities of novel non-acetal deoxoartemisinin–glycolipid hybrids.

Results and Discussion

As outlined in Chart 1, artemisinin derivative **4** was obtained through a 4 reaction sequence from either artemisinin[35)] (**2**) or artemisinic acid[36)] (**3**) according to previously reported procedures. Direct oxidation of the terminal double bond of allyl deoxoartemisinin **4** using $KMnO_4$ and $NaIO_4$ provided carboxymethyldeoxoartemisinin (**5**).[22)] Esterification of acid **5** with methanol in the presence of H_2SO_4 afforded ester **6** in 97% yield. β-isomer **6** (12*S*) in natural configuration was exclusively obtained ($J_{12,11}$=4.7 Hz).

In order to examine the role of the hybrid glycolipid linkage, different glycolipids were synthesized (Chart 2). Briefly, in the course of the stereospecific total synthesis of daumone (**1**) *via* eight steps from L-rhamnose,[1)] intermediate **7a** had been prepared. Debenzoylation of compound **7a** with NaOMe provided dihydroxy **7b**[1)] in 91% yield. Protection of the alcohol moiety of 4-(hydroxymethyl)benzoic acid (**8a**) using *tert*-butyl dimethylsilyl chloride and imidazole as nucleophilic cat-

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# These authors contributed equally to this work.

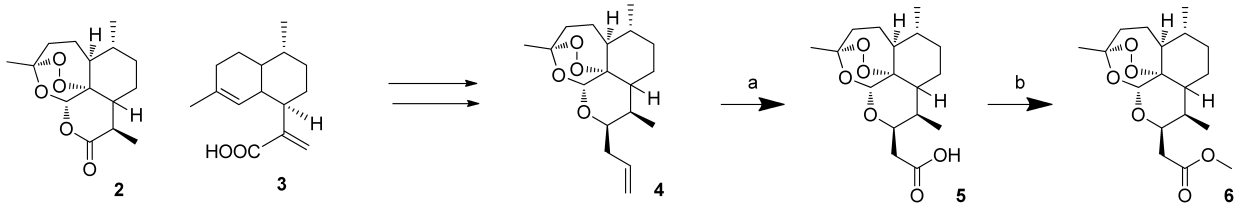
* To whom correspondence should be addressed. e-mail: mjung@yonsei.ac.kr

alyst provided compound **8b**.[22] The coupling reaction between compounds **7b** and **8b** using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 4-dimethylaminopyridine (DMAP) as previously presented afforded benzoylated lipids **9a**, **10**, and **11a**.[22] Silyl ether deprotection of compounds **9a** and **11a** using tetrabutylammonium fluoride gave compounds **9b** (94% yield) and **11b** (49% yield) as linkers, respectively.

The route used for the preparation of deoxoartemisinin–glycolipid hybrids **12**, **13**, and **14** according to the previously described method is illustrated in Chart 3.[22] Coupling of carboxymethyl deoxoartemisinin (**5**) with functionalized daumone precursor **7b** by esterification using EDC and DMAP afforded compounds **12** (22% yield), **13** (20% yield), and **14** (32% yield). The absolute configurations of C1-H and C2-H of L-rhamnose of the hybrid **12** and C3-H and C4-H of that of the hybrid **13** were assigned as *cis* diequatorial and *trans* diaxial as shown in stuctures **12** and **13**, respectively. In order to determine the effect of functional groups in the glycolipid portion of the hybrid on anticancer activity, we synthesized a compound library from compounds **13** and **14**. Controlled hydroboration and subsequent oxidation of compound **13** using 9-BBN and H_2O_2–NaOH provided alcohol **15** (70% yield). Mesylation of compound **15** as previously described followed by addition of sodium azide provided hybrid azide **16** (57%). A click reaction between azide **16** and 4′-(2-propynyloxy)-acetophenone initiated by $CuSO_4 \cdot 5H_2O$ and sodium ascorbate provided triazole **17** (32% yield). Ozonolysis of compound **13** followed by reduction with sodium borohydride gave alcohol **18** (75% yield). Mesylation of compound **18** using mesylate chloride with triethylamine as base followed by substitution using lithium bromide provided bromide **19** (79% yield). Bromide substitution of compound **19** with mercaptopyridine in the presence of potassium carbonate gave compound **20** (85% yield). A controlled ozonolysis of hybrid **14** provided the isolable ozonide **21** (75% yield). Direct one-step oxidation of compound **14** using sodium periodate and potassium permanganate gave acid **22** (52% yield).

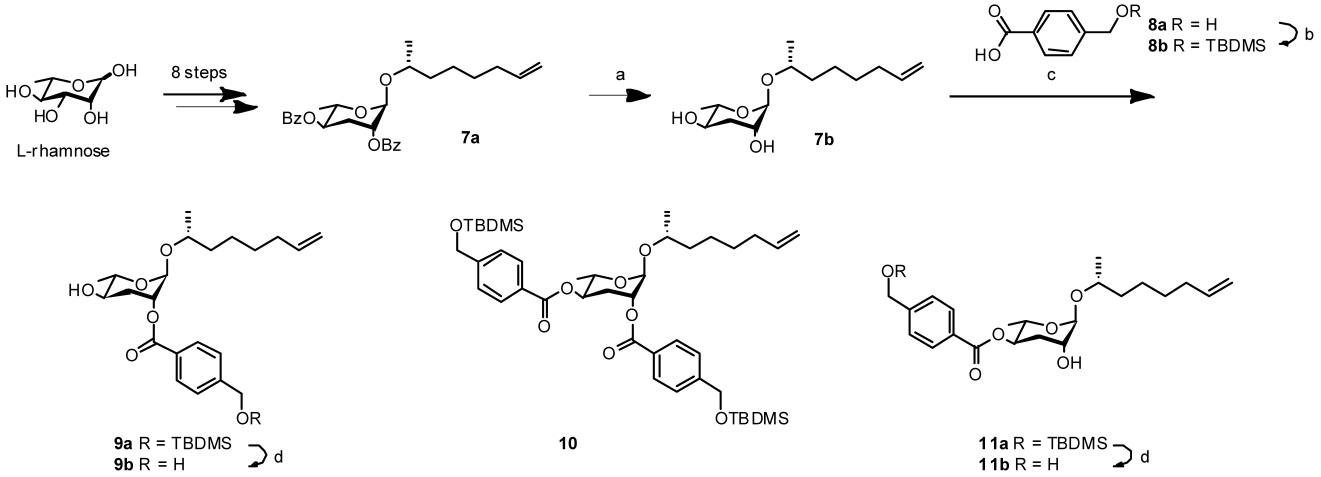
The synthesis of further deoxoartemisinin–glycolipid hybrids from glycolipids **9b** and **11b** are shown in Chart 4. The coupling reaction between carboxymethyldeoxoartemisinin (**5**) and glycolipid **9b** using EDC and DMAP provided the 4-(hydroxymethyl)benzoic acid-linked hybrids **23** and **24** (55%). Coupling between compound (**5**) and glycolipid **11b** using the same conditions provided hybrid **25** (61% yield).

In vitro anticancer activities of deoxoartemisinin–glycolipid hybrids **16**–**23** and **25**, along with daumone (**1**), artemisinin (**2**), and artemisinin derivative **6** were tested against the cancer cell lines MDA-MB-231, MCF-7, A549, HSC-2, and Ca.9-22 using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) colorimetric method. The results of these assays are summarized in Table 1. The drug standard used for comparison was cisplatin. Under our conditions, artemisinin (**2**) and its derivative (**6**) as well as daumone (**1**) failed to show notable activity at concentrations below 50 μM. However, deoxoartemisinin–glycolipid hybrids showed more potent activity than either glycolipid or artemisinin alone. Among the hybrid compounds, **17** and **18** did not exhibit notable anticancer activity. An alcohol or triazole function seems to interfere with the anticancer activity in these cancer cell lines. However, the other hybrids exhibited good anticancer activity, even better than cisplatin in specific cell lines. The



Reagents and conditions: Yields: (a) $KMnO_4$, $NaIO_4$, H_2O–acetone (1 : 1), rt, 12 h, 99%; (b) H_2SO_4, MeOH, N_2, reflux, 9 h, 97%.

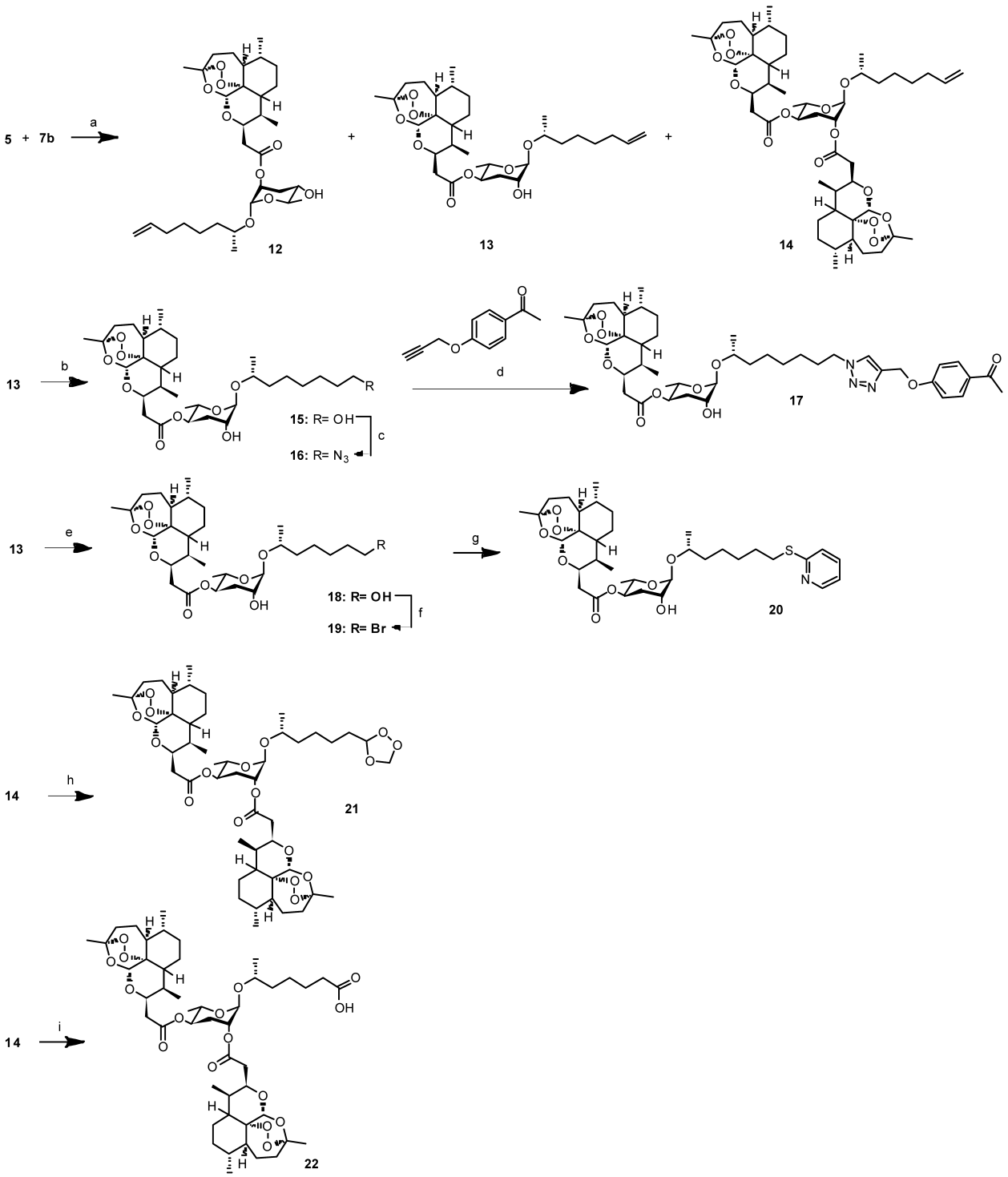
Chart 1



Reagents and conditions: Yeilds: (a) NaOMe, amberlite resin (H^+), MeOH, rt, 12 h, 91%; (b) imidazole, TBDMSCI, DMF, rt, 4 h, 31%; (c) EDC, DMAP, DMF, rt, 24 h, **9a** (10%), **10** (19%), **11a** (27%); (d) TBAF, THF–H_2O (20 : 1), rt, 24 h, **9b** (74%), **11b** (49%).

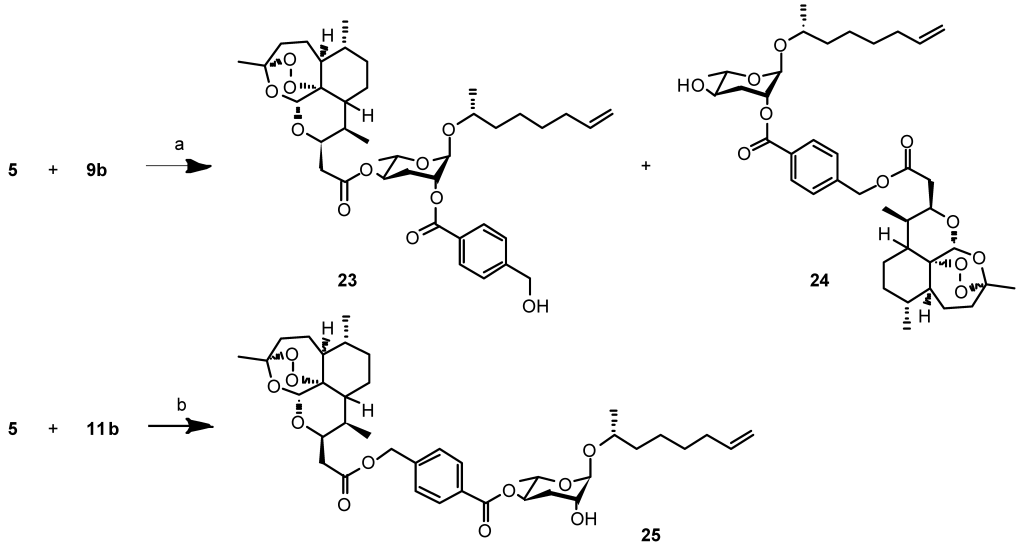
Chart 2

4-(methoxy)benzoic acid linker between deoxoartemisinin and the glycolipid in hybrid **25** increased the anticancer activity, with the metastatic breast cancer cell line (MDA-MB-231) in which the cytotoxicity was approximately five times greater than cisplatin with a IC_{50} value of 11.8 μM. For the metastatic breast cancer cell line, all of the hybrid compounds **16**, **20**, **21**, **22**, and **25** showed better activity than the reference, particularly the dimeric hybrids **21** and **22** with superior IC_{50} values of 10 μM. For the breast (MCF-7) cancer cell line, hybrids **19** and **20** showed greater than 5 times higher anticancer activity than cisplatin. In the lung cancer cell line (A549), hybrids **16**, **19**, and **20** showed 5 to 6 times more potent anticancer activity than the reference at concentrations of 9.7, 8.1, and 6.8 μM, respectively. For the oral squamous (mouth origin) carcinoma



Reagents and conditions: Yields: (a) EDC, DMAP, DMF, rt, 12 h, **12** (22%), **13** (20%) and **14** (34%); (b) 9-BBN, THF, rt, 1 h, 70%; (c) MsCl, Et_3N, CH_2Cl_2, 10 min, NaN_3, DMF, 60°C, 10 h, 57%; (d) $CuSO_4 \cdot 5H_2O$, NaAsc, CH_2Cl_2–H_2O (1 : 1, v/v), rt, 1 h, 32%; (e) O_3, CH_2Cl_2 −78°C, 5 min, $NaBH_4$, THF–MeOH (1 : 1, v/v), 0°C, 8 h, 60%; (f) MsCl, Et_3N, CH_2Cl_2, rt, 10 min, LiBr, acetone, reflux, 10 h, 79%; (g) K_2CO_3, percaptopyridine, acetone, reflux, 10 h, 85%; (h) O_3, CH_2Cl_2, −78°C, 5 min, 75%; (i) $NaIO_4$, acetone–H_2O (1 : 1, v/v), rt, 4 h, 52%.

Chart 3



Reagents and conditions: Yields: (a) EDC, DMAP, DMF, rt, 24 h, **23** (17%), **24** (55%); (b) EDC, DMAP, DMF, rt, 24 h, 61%.

Chart 4

Table 1. Cytotoxic Activities of Deoxoartemisinin–Glycolipid Hybrids (**1**, **2**, **6**, **16**–**23**, **25**) against Five Human Cancer Cell Lines

Compounds	IC_{50} values (μM)				
	MDA-MB-231	MCF-7	A549	HSC-2	Ca.9-22
Artemisinin (**1**)	>50	>50	>50	>50	>50
Daumone (**2**)	>50	>50	>50	>50	>50
6	>50	>50	>50	>50	>50
16	21.7	32.9	9.7	5.4	33.7
17	>50	>50	>50	>50	>50
18	>50	>50	>50	>50	>50
19	>50	9.2	8.1	5.4	34.6
20	48.0	8.8	6.8	5.4	29.0
21	6.4	>50	43.9	16.0	>50
22	6.7	46.4	20.7	5.5	>50
23	>50	>50	>50	>50	>50
25	11.8	>50	>50	>50	>50
Cisplatine	>50	>50	>50	11.3	8.1

MDA-MB-231: metastatic breast cancer cells (estrogen receptor-negative); MCF-7: breast cancer cells (estrogen receptor-positive); A549: lung cancer cells; HSC-2: oral squamous carcinoma cells (gingival origin); Ca.9-22: oral squamous carcinoma cell (mouth origin).

cell line (Ca.9-22), deoxoartemisinin–glycolipid hybrids **16**, **19**, and **20** showed anticancer activity with IC_{50} values between 34.6 and 29.0 μM, which reflect weaker potency than cisplatin. However, for the oral squamous (gingival origin) carcinoma cell line (HSC-2), the mono or di-deoxoartemisinin–glycolipid hybrids **16**, **19**, **20**, and **22** with IC_{50} values below 5.5 μM, generally showed greater than two fold anti-oral cancer activity compared to cisplatin. As expected, the anticancer activities of the hybrids were much more potent than the individual components artemisinin or glycolipid. However, the aromatic ring-linked hybrids (**23**, **25**) exhibited weaker activities than non-linked types. The chemical functions from the glycolipid terminal double bond seem to play an important role in enhancing anticancer activity. The best results were obtained with azide, bromide, thiol, trioxolane, and acid groups.

Conclusion

In conclusion, ten new non-acetal deoxoartemisinin–glycolipid hybrids were synthesized, which showed potent anti-oral and anti lung cancer activity. It is also noteworthy that the hybrid compounds generally showed dramatic increases in anticancer activity compared with the non-coupled molecules daumone (**1**) or artemisinin (**2**) and also compared with cisplatin. The deoxoartemisinin–glycolipid hybrids deserve further evaluation as possible anti-oral and anti-lung cancer drug candidates.

Experimental

Chemistry All commercial reagents and solvents were used as received without further purification unless otherwise indicated. Reaction solvents were distilled from calcium hydride for dichloromethane and from sodium metal and benzophenone for tetrahydrofuran. Air- and moisture-sensitive reactions were carried out in oven dried sealed glassware under a positive pressure of dry nitrogen. The reactions were monitored and the *Rf* values were determined using analytical thin layer chromatography (TLC) with Merck silica gel 60 and F_{254} precoated plates (0.25-mm thickness). Spots on the TLC plates were visualized using ultraviolet light (254 nm) and a basic potassium permanganate solution or cerium sulfate/ammonium dimolybdate/sulfuric acid solution followed by heating on a hot plate. Flash column chromatography was performed with Merck silica gel 60 (230–400 mesh). ^{1}H-NMR spectra were recorded on Bruker DRX-250 or Bruker DRX-400 NMR spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.00). Data were reported as follows: chemical shift (δ, ppm), integration, multiplicity (s=singlet, brs=broad singlet, d=doublet, t=triplet, q=quartet, and m=multiplet), coupling constants (J, Hz). ^{13}C-NMR spectra were recorded on Bruker DRX-250 (63 MHz) or Bruker DRX-400 (100 MHz) NMR spectrometers with complete proton decoupling. Carbon chemical shifts were reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). High resolution-mass spectrometer (HR-MS) analyses were

recorded on a JEOL JMS-700 analyzer spectrometer (FAB). Matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) masses were recorded on an Applied Biosystems 4700 proteomics analyzer spectrometer.

Synthesis of 10*β*-(Methylethanoate) Deoxoartemisinin 6 To a stirred solution of carboxylic acid **5**[22] (600 mg, 2.32 mmol) in 40 mL of MeOH under nitrogen H_2SO_4 (150 μL, 2.78 mmol) was added. The mixture was stirred and heated to reflux for 9 h. After completion (TLC), the mixture was cooled to room temperature and EtOAc (40 mL) was added. The reaction mixture was treated with a saturated solution of $NaHCO_3$ until basic. The aqueous phase was extracted with EtOAc (3×20 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated in reduced pressure. The product was purified by flash column chromatography on silica gel with hexane–EtOAc (3 : 2, v/v) as eluant to give compound **6** (770 mg, 97%) as a colorless oil. Compound **6**: $[\alpha]_D^{20}$ +143 (c=0.03, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 5.21 (1H, s), 4.70 (1H, m), 3.59 (3H, s), 2.67–2.46 (2H, m), 2.34 (1H, dd, J=15.1, 3.9 Hz), 2.21 (1H, td, J=13.7, 3.6 Hz), 2.02–1.34 (7H, m), 1.30 (3H, s), 1.28–1.04 (3H, m), 0.85 (3H, d, J=5.8 Hz), 0.76 (3H, d, J=7.6 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 172.0, 103.1, 89.1, 80.8, 71.4, 52.1, 51.8, 44.1, 37.4, 36.4, 35.8, 34.3, 29.7, 25.9, 24.7, 24.6, 20.1, 12.9; MALDI-TOF MS: Found 363.1594 $[M+Na]^+$. HR-MS (FAB) Calcd for $C_{18}H_{29}O_6$ $[M+H]^+$ m/z 341.1964, Found 341.1965. IR.

Synthesis of Deoxoartemisinin–Glycolipid Hybrids 12, 13, and 14 To a stirred solution of 12-carboxymethyldeoxoartemisin **5**[22] (0.48 g, 1.47 mmol), EDC (2.82 g, 14.71 mmol) and DMAP (1.80 g, 14.71 mmol) in *N*,*N*-dimethylformamide (DMF) (10 mL), compound **7b**[1] (0.38 g, 1.47 mmol) was added and stirred at room temperature for 12 h. After completion (TLC), the reaction mixture was quenched with slow addition of satured citric acid (10 mL). The organic phase was extracted with EtOAc (3×10 mL) and washed with brine (3×10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in reduced pressure. The product was purified by flash columns chromatography on silica gel with EtOAc as eluant to give compound **12** (0.18 g, 0.32 mmol, 22%), compound **13** (0.16 g, 0.28 mmol, 20%), and compound **14** (0.22 g, 0.25 mmol, 34%). Compound **12**: $[\alpha]_D^{20}$ +14 (c=0.1, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 0.87 (d, J=7.58 Hz, 3H), 0,96 (d, J=5.37, 3H), 1.07–1.24 (m, 4H), 1.12 (d, J=6.32 Hz, 3H), 1.21 (d, J=6.00 Hz, 3H), 1.40 (s, 3H), 1.48–2.23 (m, 17H), 2.24–2.56 (m, 2H), 2.60–2.84 (m, 2H), 3.72–3.85 (m, 2H), 3.89 (m, 1H), 4.67–4.82 (m, 1H), 4.71 (s, 1H), 4.83–4.92 (m, 1H), 4.95 (d, J=10.23 Hz, 1H), 5.00 (d, J=16.94 Hz, 1H), 5.32 (s, 1H), 5.82 (tdd, J=16.94, 10.23 Hz, 1H): IR (KBr, cm^{-1}) ν_{max} 3473, 2927, 2873, 2360, 2342, 1736, 1463, 1373, 1202, 1130, 1103, 1039; HR-MS (FAB) Calcd for $C_{31}H_{50}NaO_9$ $[M+Na]^+$ m/z 589.3353, Found 589.3377. *Anal.* Calcd for $C_{31}H_{50}O_9$: C, 65.72; H, 8.83. Found: C, 65.74; H, 8.91. Compound **13**. $[\alpha]_D^{20}$ +22 (c=0.1, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 0.87 (d, J=7.58 Hz, 3H,) 0.97 (d, J=5.69 Hz, 3H), 1.11 (d, J=6.00 Hz, 3H), 1.16–1.27 (m, 4H), 1.28 (d, J=5.69 Hz, 3H), 1.41 (s, 3H), 1.49–2.23 (m, 17H), 2.25–2.49 (m, 2H), 2.61–2.83 (m, 1H), 3.58–3.85 (m, 3H), 3.63–3.71 (m, 1H), 4.70–4.82 (m, 1H), 4.73 (s, 1H), 4.91 (br s, 1H), 4.94 (d, J=10.19 Hz, 1H), 5.00 (d, J=16.98 Hz, 1H), 5.34 (s, 1H), 5.70–5.93 (tdd, J=16.98, 10.19 Hz, 1H). IR (KBr, cm^{-1}) ν_{max} 2924, 2851, 2369, 2337, 1734, 1456, 1368: HR-MS (FAB) Calcd for $C_{31}H_{49}O_9$ $[M+H]^+$ m/z 567.9899, Found 567.9833. *Anal.* Calcd for $C_{31}H_{49}O_9$: C, 65.84; H, 8.67. Found: C, 65.79; H, 8.66. Compound **14**. $[\alpha]_D^{20}$ +47 (c=0.1, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 5.72–5.92 (1H, m), 5.29–5.37 (2H, m), 4.83–5.08 (4H, m), 4.75 (3H, m), 3.66–3.96 (2H, m), 2.58–2.88 (4H, m), 2.42–2.59 (2H, m), 2.23–2.41 (2H, m), 1.41 (6H, s), 1.24–2.21 (30H, m), 1.20 (3H, d, J=6.0 Hz), 1.12 (3H, d, J=5.8 Hz), 0.97 (6H, d, J=5.4 Hz), 0.87 (6H, d, J=7.3 Hz). ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 170.6, 138.9, 114.4, 103.8, 103.3, 92.9, 88.9, 88.8, 80.9, 80.8, 77.5, 77.0, 76.5, 72.5, 71.7, 71.1, 70.7, 69.9, 66.7, 52.3, 44.3, 37.3, 36.8, 36.5, 36.4, 35.5, 34.4, 33.9, 29.6, 26.0, 25.7, 25.1, 24.8, 20.2, 19.2, 17.7, 14.1, 13.2; MALDI-TOF MS: Found 897.5077 $[M+Na]^+$. Calcd 874.5123 for $C_{48}H_{74}O_{14}$.

Synthesis of Deoxoartemisinin–Glycolipid Hybrid 16 Under N_2 atmosphere, a 9-BBN solution in tetrahydrofuran (THF) (0.5 M, 0.16 mmol) was added to the hybrid **13** (47.0 mg, 0.083 mmol) and the mixture was stirred for 1 h at room temperature. After the conversion was completed (TLC), H_2O_2–NaOH (3 N) (1 : 1, v/v) solution was added until pH 7–8. EtOAc (10 mL) was added and the organic layer was washed with $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by silica gel column chromatography using hexane–EtOAc (1 : 1, v/v) to give compound **15** (33.1 mg, 0.058 mmol, 70%). Mesylate chloride (5.4 L, 0.069 mmol) was added to a stirred solution of compound **15** (33.1 mg, 0.058 mmol) and triethylamine (16.0 L, 0.116 mmol) in dry CH_2Cl_2 (5 mL) at room temperature. When TLC showed that starting material was completely disappeared (10 min), the reaction was quenched by addition of water (10 mL). The organic layer was extracted with EtOAc (3×10 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. NaN_3 (7.5 mg, 0.116 mmol) in DMF (5 mL) was added to the crude, stirred and warmed at 60°C for 10 h. On completion (TLC), the reaction mixture was washed with NH_4Cl (10 mL). The organic layer was extracted with EtOAc (3×10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The product was purified by silica gel column chromatography using hexane–EtOAc (1 : 1, v/v) as eluant to give compound **16** (20.2 mg, 0.033 mmol, 57%) as a colorless syrup. Compound **16**: $[\alpha]_D^{20}$ −81 (c=0.08, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 5.31 (1H, s), 4.97–4.84 (1H, m), 4.80–4.69 (2H, m), 3.95–3.72 (3H, m), 3.27 (2H, t, J=6.79 Hz), 2.83–2.61 (2H, m), 2.47 (1H, dd, J=15.0, 4.3 Hz), 2.32 (1H, td, J=13.8, 3.8 Hz), 2.18–1.42 (22H, m), 1.39 (3H, s), 1.21 (3H, d, J=6.3 Hz), 1.12 (3H, d, J=6.0 Hz), 0.96 (3H, d, J=5.8 Hz), 0.86 (3H, d, J=7.6 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 170.9, 103.4, 96.4, 89.1, 81.0, 72.1, 71.8, 70.4, 69.0, 67.4, 52.4, 51.6, 44.4, 37.6, 37.2, 36.6, 34.6, 32.2, 29.8, 29.3, 29.0, 26.8, 26.1, 25.7, 24.8, 20.3, 19.1, 17.8, 13.2; MALDI-TOF MS: Found 632.3568 $[M+Na]^+$. HR-MS (FAB) Calcd for $C_{31}H_{52}N_3O_9$ $[M+H]^+$ m/z 610.3704, Found 610.3694.

Synthesis of Deoxoartemisinin–Glycolipid Hybrid 17 4′-(Propagyloxy)acetophenone (2.9 mg 0.016 mmol) was added to a solution of **16** (10.0 mg, 0.016 mmol), $CuSO_4 \cdot 5H_2O$ (4.1 mg, 0.016 mmol) and sodium ascorbate (6.5 mg, 0.033 mmol) in CH_2Cl_2–H_2O (5 mL, 1 : 1, v/v) for 1 h. On completion (TLC), brine was added (10 mL) and the organic phase was extracted with EtOAc (3×10 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The product was purified by silica gel column chromatography using hex-

ane–EtOAc (1 : 1, v/v) as eluant to give **17** (4 mg, 0.005 mmol, 32%). Compound **17**: $[\alpha]_D^{20}$ −32 (c=0.06, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.00–7.91 (2H, m), 7.62 (1H, s), 7.08–7.00 (2H, m), 5.31 (1H, s), 5.28 (2H, s), 4.97–4.83 (1H, m), 4.80–4.68 (2H, m), 4.37 (2H, t, J=7.0 Hz), 3.92–3.70 (3H, m), 2.81–2.62 (2H, m), 2.55 (3H, s), 2.53–2.43 (1H, m), 2.39–2.25 (1H, m), 2.16–1.43 (22H, m), 1.38 (3H, s), 1.20 (3H, d, J=6.2 Hz), 1.11 (3H, d, J=6.0 Hz), 0.95 (3H, d, J=4.4 Hz), 0.85 (3H, d, J=7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 196.7, 170.7, 162.0, 143.4, 130.7, 130.6, 122.6, 114.4, 103.3, 96.3, 88.9, 80.9, 71.9, 71.7, 70.2, 68.8, 67.3, 62.1, 52.2, 50.5, 44.2, 37.4, 37.0, 36.5, 36.4, 34.4, 32.0, 30.3, 29.7, 29.6, 29.0, 26.4, 25.9, 25.4, 24.7, 20.2, 19.0, 17.7, 13.1; MALDI-TOF MS: Found 806.3607 $[M+Na]^+$. HR-MS (FAB) Calcd for $C_{42}H_{62}N_3O_{11}$ $[M+H]^+$ m/z 784.4384, Found 784.4388.

Synthesis of Deoxoartemisinin–Glycolipid Hybrid 18 A solution of compound **13** (100 mg, 0.176 mmol) in dry CH_2Cl_2 (10 mL) was flushed with N_2 and then subjected to a steady stream of O_3 at −78°C until the solution became saturated and appeared blue. Excess O_3 was flushed out from the solution with N_2 and the solvent removed under reduced pressure. THF–MeOH (20 mL, 1 : 1, v/v) was added and the solution was carefully treated with excess of sodium tetrahydroborate (66.0 mg, 1.76 mmol) at 0°C for 8 h. The resulting mixture was concentrated under reduced pressure, followed by addition of water (5 mL) and EtOAc (10 mL). The organic layer was extracted by EtOAc (3×10 mL), dried over $MgSO_4$, filtered and solvent evaporated under reduced pressure. The crude product was purified by flash silica gel column chromatography using hexane–EtOAc (3 : 2, v/v) as eluant to give compound **18** (54 mg, 0.095 mmol, 60%) as a colorless syrup. Compound **18**. $[\alpha]_D^{20}$ −13 (c=0.1, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$), δ: 5.29 (1H, s), 4.95–4.82 (1H, m), 4.76–4.66 (2H, m), 3.93–3.72 (3H, m), 3.63 (2H, t, J=6.6 Hz), 2.80–2.60 (2H, m), 2.45 (1H, dd, J=15.0, 4.4 Hz), 2.30 (1H, td, J=13.8, =3.7 Hz), 2.14–1.40 (20H, m), 1.37 (3H, s), 1.19 (3H, d, J=6.3 Hz), 1.10 (3H, d, J=6.2 Hz), 0.94 (3H, d, J=5.8 Hz), 0.84 (3H, d, J=7.6 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 170.7, 103.3, 96.2, 88.9, 80.8, 71.9, 71.8, 70.5, 68.9, 67.3, 62.9, 52.4, 44.4, 37.6, 37.2, 36.6, 34.6, 32.8, 32.1, 29.7, 26.0, 25.8, 25.6, 24.8, 20.3, 19.1, 17.8, 13.2; MALDI-TOF MS: Found 593.3291 $[M+Na]^+$. HR-MS (FAB) Calcd for $C_{30}H_{51}O_{10}$ $[M+H]^+$ m/z 571.3482, Found 571.3470.

Synthesis of Deoxoartemisinin–Glycolipid Hybrid 19 Mesylate chloride (8 μL, 0.104 mmol) was added to a stirred solution of compound **18** (54.0 mg, 0.095 mmol) and triethylamine (27 μL, 0.189 mmol) in dry CH_2Cl_2 (5 mL) at room temperature. When TLC showed that starting material was completely disappeared (10 min), the reaction was quenched by addition of water (10 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The crude was added to a stirred solution of LiBr (24.7 mg 0.284 mmol) in acetone (5 mL) and the mixture was refluxed. On completion (TLC), the reaction was quenched with brine (10 mL). The organic layer was extracted with EtOAc (3×10 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The product was purified by silica gel column chromatography using hexane–EtOAc (1 : 1, v/v) to give compound **19** (47.1 mg, 0.074 mmol, 79%) as a colorless syrup. $[\alpha]_D^{20}$ +40 (c=0.02, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 5.30 (1H, s), 4.96–4.83 (1H, m), 4.79–4.67 (2H, m), 3.93–3.71 (3H, m), 3.41 (2H, t, J=6.9 Hz), 2.83–2.59 (2H, m), 2.45 (1H, dd, J=15.0, 4.3 Hz), 2.31 (1H, td, J=14.4, 3.6 Hz), 2.18–1.40 (20H, m), 1.38 (3H, s), 1.20 (3H, d, J=6.3 Hz), 1.12 (3H, d, J=6.2 Hz), 0.95 (3H, d, J=5.7 Hz), 0.85 (3H, d, J=7.4 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 170.9, 103.4, 96.4, 89.1, 81.0, 71.9, 71.8, 70.4, 68.9, 67.4, 52.4, 44.4, 37.6, 37.1, 36.6, 34.6, 33.9, 32.8, 32.1, 29.7, 28.3, 26.0, 24.9, 24.8, 20.3, 19.1, 17.8, 13.2; MALDI-TOF MS: Found 655.3136 $[M+Na]^+$. HR-MS (FAB) Calcd for $C_{30}H_{50}BrO_9$ $[M+H]^+$ m/z 633.2638, Found 633.2636.

Synthesis of Deoxoartemisinin–Glycolipid Hybrid 20 A solution of compound **19** (27.0 mg, 0.043 mmol), K_2CO_3 (17.7 mg 0.128 mmol) and mercaptopyridine (4.7 mg 0.043 mmol) in acetone (10 mL) was stirred at reflux. On completion (TLC), brine (10 mL) was added. The organic layer was extracted with EtOAc (3×10 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The product was purified by silica gel column chromatography using hexane–EtOAc (1 : 1, v/v) to give compound **20** (24.2 mg, 0.036 mmol, 85%) as a colorless syrup. $[\alpha]_D^{20}$ −45 (c=0.1, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.44–8.37 (1H, m), 7.50–7.41 (1H, m), 7.19–7.12 (1H, m), 6.95 (1H, ddd, J=7.27, 5.0, 1.0 Hz), 5.30 (1H, s), 4.89 (1H, m), 4.79–4.67 (2H, m), 3.94–3.71 (3H, m), 3.16 (2H, t, J=7.4 Hz), 2.81–2.59 (2H, m), 2.44 (1H, J=15.0, 4.4 Hz), 2.39–2.24 (1H, m), 2.18–1.41 (20H, m), 1.38 (3H, s), 1.20 (3H, d, J=6.3 Hz), 1.11 (3H, d, J=6.0 Hz), 0.94 (3H, d, J=5.8 Hz), 0.84 (3H, d, J=7.4 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 170.8, 149.4, 135.8, 122.2, 119.2, 103.2, 96.3, 89.0, 80.8, 71.9, 71.6, 70.3, 68.8, 67.2, 52.3, 44.3, 37.4, 37.0, 36.5, 36.4, 34.5, 32.0, 30.0, 29.6, 29.4, 28.9, 25.9, 25.3, 24.7, 24.7, 20.2, 19.0, 17.7, 13.0; MALDI-TOF MS: Found 686.3982 $[M+Na]^+$. HR-MS (FAB) Calcd for $C_{35}H_{54}NO_9S$ $[M+H]^+$ m/z 664.3519, Found 664.3522.

Synthesis of Deoxoartemisinin–Glycolipid Hybrid 21 A solution of compound **14** (50.0 mg, 0.057 mmol) in dry CH_2Cl_2 (10 mL) was flushed with N_2 and then subjected to a steady stream of O_3 at −78°C until the solution became saturated and appeared blue. After the reaction completed, excess O_3 was flushed out from the solution with N_2 and the solvent removed under reduced pressure. The product was purified by silica gel column chromatography using hexane–EtOAc (3 : 2, v/v) as eluant to give compound **21** (39.3 mg, 0.043 mmol, 75%). $[\alpha]_D^{20}$ +50 (c=0.1, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 5.33 (1H, s), 5.32 (1H, s), 5.21 (1H, s), 5.14 (1H, d, J=4.8 Hz), 5.05 (1H, s), 4.99–4.85 (2H, m), 4.84–4.66 (3H, m), 3.95–3.80 (1H, m), 3.78–3.65 (1H, m), 2.89–2.61 (4H, m), 2.57–2.42 (2H, m), 2.41–2.23 (2H, m), 2.22–1.46 (30H, m), 1.41 (6H, s), 1.20 (3H, d, J=6.2 Hz), 1.12 (3H, d, J=6.0 Hz), 0.97 (6H, d, J=5.7 Hz), 0.87 (6H, d, J=7.4 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 170.9, 170.6, 103.6, 103.3, 103.3, 94.0, 93.4, 88.9, 88.8, 80.8, 72.2, 71.8, 71.6, 70.8, 69.9, 66.9, 52.3, 52.2, 44.3, 44.2, 37.4, 37.3, 36.8, 36.4, 35.4, 34.4, 31.1, 29.6, 29.5, 25.9, 25.4, 24.7, 24.6, 24.5, 23.8, 20.2, 19.0, 17.7, 13.2, 13.1; HR-MS (FAB) Calcd for $C_{48}H_{74}O_{17}$ $[M+H]^+$ m/z 923.5004, Found 923.5002.

Synthesis of Deoxoartemisinin–Glycolipid Hybrid 22 In a stirred solution of compound **14** (100 mg, 0.114 mmol) in acetone–water (1 : 1, v/v, 20 mL) was added sodium periodate (16 mg, 0.075 mmol) and potassium permanganate (72 mg, 0.457 mmol) at room temperature. After completion (4 h, TLC), the solvent was evaporated. Water (10 mL) and EtOAc (10 mL) were added and the organic phase was extracted with EtOAc (3×10 mL). The crude product was purified by flash silica gel

column chromatography using hexane–EtOAc (1 : 1, v/v) as eluant to compound **22** (52.7 mg, 0.059 mmol, 52%). $[\alpha]_D^{20}$ +69 (c=0.06, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 5.41 (1H, s), 5.33 (1H, s), 5.03–4.69 (5H, m), 3.99–3.68 (2H, m), 2.92–2.61 (4H, m), 2.61–2.23 (6H, m), 2.22–1.46 (28H, m), 1.41 (6H, s), 1.24 (3H, d, J=6.8 Hz), 1.12 (3H, d, J=5.7 Hz), 0.97 (6H, d, J=5.4 Hz), 0.88 (6H, d, J=6.6 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 170.9, 170.6, 103.8, 103.3, 92.9, 88.8, 88.7, 80.9, 80.8, 72.5, 71.7, 71.1, 70.7, 69.9, 66.9, 52.3, 44.3, 37.7, 36.8, 36.5, 36.4, 35.5, 34.4, 33.9, 29.6, 26.0, 25.7, 25.1, 24.8, 20.2, 19.2, 17.7, 14.1, 13.2; MALDI-TOF MS: Found 915.5246 $[M+Na]^+$. HR-MS (FAB) Calcd for $C_{47}H_{73}O_{16}$ $[M+H]^+$ m/z 893.4899, Found 893.4873.

Synthesis of Glycolipid Derivatives 9a, b, 10, and 11a, b A solution of compound **8b**[22] (86 mg, 0.32 mmol), EDC (618 mg, 3.2 mmol) and DMAP (394 mg, 3.2 mmol) in DMF (5 mL) was combined with compound **7b**[1] (100 mg, 0.39 mmol) at room temperature. The reaction mixture was stirred for 24 h. After completion (TLC), the reaction mixture was quenched with slow addition of saturated citric acid (10 mL), extracted with EtOAc (3×5 mL) and washed with brine (10 mL). Organic layers were combined and dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude products were purified by flash column chromatography on silica gel using hexane–EtOAc (2 : 2, v/v) as eluant to give compound **9a** (16 mg, 0.03 mmol, 10%), compound **10** (23.1 mg, 0.3 mmol, 19%) and compound **11a** (43.3 mg, 0.08 mmol, 27%) as white powders. Compound **9a**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.01 (2H, d, J=8.1 Hz), 7.39 (2H, d, J=8.1 Hz), 5.74–5.90 (1H, m), 4.91–5.22 (3H, m), 4.84–4.91 (1H, m), 4.80 (2H, s), 3.63–3.87 (3H, m), 2.15–2.26 (1H, m), 1.94–2.13 (3H, m), 1.55–1.71 (2H, m), 1.36–1.52 (4H, m), 1.32 (3H, d, J=5.9 Hz), 1.15 (3H, d, J=6.0 Hz), 0.95 (9H, s), 0.11 (6H, s). MALDI-TOF MS: Found 529.3077 $[M+Na]^+$. Calcd 506.3149 for $C_{28}H_{46}O_6Si$. Compound **10**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.07 (2H, d, J=8.1 Hz), 8.01 (2H, d, J=8.2 Hz), 7.38–7.45 (4H, m), 5.84 (1H, m), 5.11–5.24 (2H, m), 4.92–5.11 (3H, m), 4.78–4.83 (4H, m), 4.06–4.17 (1H, m), 3.79–3.89 (1H, m), 2.36–2.45 (1H, m), 2.16–2.26 (1H, m), 2.03–2.15 (2H, m), 1.56–1.68 (2H, m), 1.37–1.56 (4H, m), 1.28 (3H, d, J=5.6 Hz), 1.19 (3H, d, J=6.0 Hz), 0.96 (9H, s), 0.95 (9H, s), 0.11 (6H, s), 0.11 (6H, s). MALDI-TOF MS: Found 777.4221 $[M+Na]^+$. Calcd 754.4323 for $C_{42}H_{66}O_8Si_2$. Compound **11a**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.04 (2H, d, J=8.1 Hz), 7.57 (2H, d, J=7.3 Hz), 5.75–5.92 (1H, m), 4.86–5.15 (3H, m), 4.75–4.83 (1H, m), 4.80 (2H, s), 3.63–3.91 (3H, m), 2.17–2.29 (1H, m), 1.96–2.15 (3H, m), 1.55–1.71 (2H, m), 1.35–1.54 (4H, m), 1.24 (3H, d, J=6.4 Hz), 1.15 (3H, d, J=6.0 Hz), 0.95 (9H, s), 0.11 (6H, s). MALDI-TOF MS: Found 529.3053 $[M+Na]^+$. Calcd 506.3149 for $C_{28}H_{46}O_6Si$. Compound **11b** ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.03 (2H, d, J=8.0 Hz), 7.58 (2H, d, J=7.2 Hz), 5.74–5.93 (1H, m), 4.87–5.14 (3H, m), 4.72–4.81 (1H, m), 4.78 (2H, s), 3.61–3.89 (3H, m), 2.17–2.27 (1H, m), 1.97–2.31 (3H, m), 1.54–1.71 (2H, m), 1.36–1.55 (4H, m), 1.23 (3H, d, J=6.5 Hz), 1.16 (3H, d, J=6.0 Hz). MALDI-TOF MS: Found 415.2107 $[M+Na]^+$. Calcd 392.2268 for $C_{22}H_{32}O_6$.

Tetrabutylammonium fluoride (89.0 mg, 0.34 mmol) was added to a solution of compound **9a** (43.3 mg, 0.085 mmol) in THF–water (5 mL, 20 : 1, v/v). The mixture was stirred for 24 h at room temperature. After completion (TLC), ether (10 mL) and water (10 mL) were added and the organic phase was washed with water (3×10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The product was purified by flash column chromatography on silica gel using EtOAc as eluant to give compound **9b** (24.8 mg, 0.063 mmol, 74%). Compound **9b**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.01 (2H, d, J=8.1 Hz), 7.42 (2H, d, J=8.1 Hz), 5.75–5.90 (1H, m), 4.91–5.12 (3H, m), 4.87 (1H, s), 4.77 (2H, br s), 3.61–3.89 (3H, m), 2.13–2.26 (2H, m), 1.94–2.13 (2H, m), 1.68–1.82 (1H, m), 1.53–1.68 (1H, m), 1.44 (4H, m), 1.32 (3H, d, J=5.9 Hz), 1.15 (3H, d, J=5.9 Hz). MALDI-TOF MS: Found 415.2137 $[M+Na]^+$. Calcd 392.2227 for $C_{22}H_{32}O_6$.

Synthesis of Deoxoartemisinin–Glycolipid Hybrids 23 and 24 To a stirred solution of **5** (23.6 mg, 0.07 mmol), EDC (139 mg, 0.72 mmol) and DMAP (88.0 mg, 0.72 mmol) in DMF (5 mL), compound **9b** (28.4 mg, 0.07 mmol) was added at room temperature and the reaction mixture was stirred for 12 h. After completion (TLC), the reaction mixture was quenched with slow addition of satured citric acid (5 mL), extracted with EtOAc (3×10 mL) and washed with brine (3×10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash columns chromatography on silica gel with hexane–EtOAc (3 : 2, v/v) as eluant to give compound **23** (8.6 mg, 0.012 mmol, 17%) and compound **24** (27.6 mg, 0.039 mmol, 55%). Compound **23**: $[\alpha]_D^{20}$ +30 (c=0.1, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.05 (2H, d, J=8.1 Hz), 7.45 (2H, d, J=8.1 Hz), 5.83 (1H, tdd, J=6.6, 17.0, 10.2 Hz), 5.35 (1H, s), 5.23 (2H, br s), 5.13–4.91 (3H, m), 4.90–4.68 (3H, m), 4.05–3.87 (1H, m), 3.86–3.74 (1H, m), 3.86–1.44 (24H, m), 1.41 (3H, s), 1.32 (3H, d, J=6.6 Hz), 1.16 (3H, d, J=6.0 Hz), 0.96 (3H, d, J=5.5 Hz), 0.87 (3H, d, J=7.4 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 171.3, 165.4, 141.3, 138.9, 129.9, 129.5, 127.5, 114.4, 103.2, 93.4, 89.0, 72.0, 80.8, 71.9, 71.7, 69.5, 68.4, 52.2, 65.6, 44.1, 37.4, 36.9, 36.4, 36.0, 34.4, 33.7, 32.7, 29.7, 28.8, 26.0, 25.2, 24.6, 20.1, 19.1, 17.7, 13.0. MALDI-TOF MS: Found 701.4027 $[M+H]^+$. HR-MS (FAB) Calcd for $C_{40}H_{63}N_2O_{10}$ $[M+H]^+$ m/z 701.3901, Found 701.3897. Compound **24**: ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 0.81–0.91 (m, 5H) 0.96 (d, J=5.84 Hz, 2H) 1.15 (d, J=6.00 Hz, 2H) 1.32 (d, J=5.84 Hz, 3H) 1.41 (s, 3H) 2.14–2.43 (m, 1H) 2.46–2.59 (m, 1H) 2.69–2.85 (m, 1H) 3.60–3.87 (m, 1H) 4.79–4.90 (m, 2H) 4.91–5.13 (m, 1H) 5.23 (d, J=4.90 Hz, 2H) 5.27–5.32 (m, 1H) 5.36 (s, 1H) 5.72–5.92 (m, 1H) 7.46 (d, J=8.06 Hz, 2H) 8.03 (d, J=8.21 Hz, 2H): ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 13.04 17.71 19.07 20.12 24.65 25.19 28.77 29.66 32.74 33.70 34.39 36.94 37.40 44.11 52.19 65.59 68.41 69.54 71.70 71.87 72.03 80.83 89.00 93.45 103.25 114.37 127.53 129.54 129.90 138.87 141.32 165.36 171.34; MALDI-TOF MS: Found 723.3771 $[M+Na]^+$. Calcd 700.3873 for $C_{39}H_{56}O_{11}$.

Synthesis of Deoxoartemisinin–Glycolipid Hybrid 25 Tetrabutylammonium fluoride (32.8 mg, 0.17 mmol) was added to a solution of compound **11a** (15.9 mg, 0.031 mmol) in THF–water (5 mL, 20 : 1 v/v). The mixture was stirred for 24 h at room temperature. After completion (TLC), ether (10 mL) and water (10 mL) were added and the organic phase was washed with water (3×10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The product was purified by flash column chromatography on silica gel using EtOAc as eluant to give compound **11b** (6.1 mg, 0.015 mmol, 49%). To a stirred solution of compound **5** (5.0 mg, 0.015 mmol), EDC (29.3 mg, 0.15 mmol) and DMAP (18.7 mg, 0.15 mmol) in DMF (5 mL),

compound **11b** (6.0 mg, 0.015 mmol) was added at room temperature and the mixture stirred for 12 h. After completion (TLC), the reaction mixture was quenched with slow addition of satured citric acid (5 mL), extracted with ethyl acetate (3×10 mL) and washed with brine (3×10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash columns chromatography on silica gel with hexane–EtOAc (3 : 2, v/v) as eluant to give compound **25** (6.5 mg, 0.009 mmol, 61%). Compound **25**: $[\alpha]_D^{20}$ −37 (c=0.03, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.01 (2H, d, J=8.1 Hz), 7.45 (2H, d, J=8.1 Hz), 5.94–5.73 (1H, m), 5.35 (1H, s), 5.29–4.74 (7H, m), 4.12–3.95 (1H, m), 3.91–3.58 (2H, m), 2.87–2.62 (2H, m), 2.52 (1H, dd, J=15.0, 3.6 Hz), 2.44–2.16 (2H, m), 2.15–1.43 (19H, m), 1.40 (3H, s), 1.23 (3H, d, J=6.6 Hz), 1.15 (3H, d, J=6.0 Hz), 0.96 (3H, d, J=5.5 Hz), 0.86 (3H, d, J=7.4 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 171.4, 165.3, 138.9, 138.2, 129.9, 129.8, 127.6, 114.4, 103.2, 96.2, 89.4, 80.9, 72.0, 71.7, 70.7, 68.9, 67.2, 65.6, 52.2, 44.1, 37.4, 37.2, 29.9, 29.7, 28.8, 26.0, 28.8, 26.0, 25.2, 24.7, 20.1, 19.1, 17.7, 13.1; MALDI-TOF MS: Found 723.3849 $[M+Na]^+$. HR-MS (FAB) Calcd for $C_{39}H_{57}O_{11}$ $[M+H]^+$ m/z 701.3901, Found 701.3889.

Biology Materials Dulbecco's modified Eagle's medium (DMEM), DMEM/F12, fetal bovine serum (FBS), RPMI1640 were purchased from Gibco BRL (Rockville, MD, U.S.A.). 3-(4,5-Dimethylthiazol-2-yl)-2,4-diphenyl-2*H*-tetrazolium bromide (MTT), dimethyl sulfoxide (DMSO), cholera toxin, hydrocortisone, insulin, transferrin, triiodothyronine (T3), and cisplatin were obtained from Sigma-Aldrich Chem. Co. (St. Louis, MO, U.S.A.).

Cell Viability Assay The viability of cancer cells was determined *via* a MTT assay. MCF-7 and MDA-MB-231 breast cancer cells were cultured in DMEM supplemented with 10% FBS in a humidified atmosphere of 5% CO_2 at 37°C, and A549 lung cancer cells were maintained in 10% FBS-RPMI1640 medium. HSC-2 and Ca9.22 oral cancer cells were cultured in DMEM–F12 (3 : 1) supplemented with 10% FBS, 1×10^{-10} M cholera toxin, 0.4 mg/mL hydrocortisone, 5 μg/mL insulin, 5 μg/mL transferrin and 2×10^{-11} M T3. The compounds were dissolved in DMSO and diluted with culture media. Cancer cells (1.0×10^4 cells/mL) were seeded onto each well of a 96-well plate with the respective media and incubated to adhere overnight. The cells were then treated with various concentrations of each compound in serum-free medium for 24 h. Twenty microliters of a MTT solution (5 mg/mL) was added to each well, and the cells were incubated for 4 h at 37°C. The medium was then removed, and 200 μL of DMSO was added to each well. The absorbance was determined at 570 nm using a microplate reader (Bio-Rad Laboratories, Hercules, CA, U.S.A.).

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