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Research paper

Synthesis and structure-activity relationship studies of water-soluble β-cyclodextrin-glycyrrhetinic acid conjugates as potential anti-influenza virus agents

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ABSTRACT

Glycyrrhetinic acid (GA) is a major constituent of the herb *Glycyrrhiza glabra*, and many of its derivatives demonstrate a broad spectrum of antiviral activities. In the current study, 18 water-soluble β-cyclodextrin (CD)-GA conjugates, in which GA was covalently coupled to the primary face of β-CD using 1,2,3-triazole moiety along with varying lengths of linker, were synthesized via copper-catalyzed azide-alkyl cycloaddition reaction. Benefited from the attached β-CD moiety, all these conjugates showed lower hydrophobicity (Alog*P*) compared with their parent compound GA. With the exception of per-*O*-methylated β-CD-GA conjugate (**35**), all other conjugates showed no significant cytotoxicity to MDCK cells, and these conjugates were then screened against A/WSN/33 (H1N1) virus using the cytopathic effect assay. The preliminary results indicated that six conjugates showed promising antiviral activity, and the C-3 and C-30 of GA could tolerate some modifications. Our findings suggested that GA could be used as a lead compound for the development of potential anti-influenza virus agents.

1. Introduction

Licorice, the roots of the perennial herb *Glycyrrhiza glabra* which are endemic to Mediterranean and certain areas of Asia, has been one of the oldest and most extensively used medicinal plants [1]. Pharmacologically active components that have been most studied include triterpenoids (3–5%), with glycyrrhizic acid (also known as glycyrrhizin, **1**) being present in the highest concentration, and flavonoids (1–1.5%) [2]. Glycyrrhizic acid (**1**), composed of one molecule of glycyrrhetinic acid (GA, **2**) and two molecules of glucuronic acid (Fig. 1), can be hydrolyzed by β-glucuronidases in the intestinal bacteria [3]. The amount of **2** in licorice root is reported to be within the range of 0.1–1.6%, depending on species and growing region [4]. Compounds **1** and **2** have attracted considerable attention from chemists and pharmacologists because of their pharmacological and biological effects, such as anti-inflammatory, antitumor, antiviral and other activities [1,5].

A lot of studies have confirmed the antiviral activity of glycyrrhizic acid (**1**). In Japan, compound **1** has been used in the treatment of chronic viral hepatitis for more than 40 years as the intravenous drug Stronger Neo-Minophagen C (SNMC). It has shown that the administration of SNMC to patients with hepatitis C virus infection lowers the serum transaminase activity, even in the patients resistant to the interferon therapy [6]. Pompei et al. have reported that compound **1** can inhibit many DNA and RNA viruses, including HBV, HIV and EBV *in vitro* [7]. The antiviral activities of compound **1** against SARS-associated corona virus and influenza virus have also been demonstrated [8,9]. Recently, it has been noted that the application of compound **1** as a potential antiviral agent can be further improved by using certain drug delivery systems, e.g., mucoadhesive nanoparticles based on poly (methyl vinyl ether-co-maleic anhydride) (PVM/MA) [10].

Compared with glycyrrhizic acid (**1**), studies of the antiviral activity of its aglycone **2** are limited, but have attracted increasing

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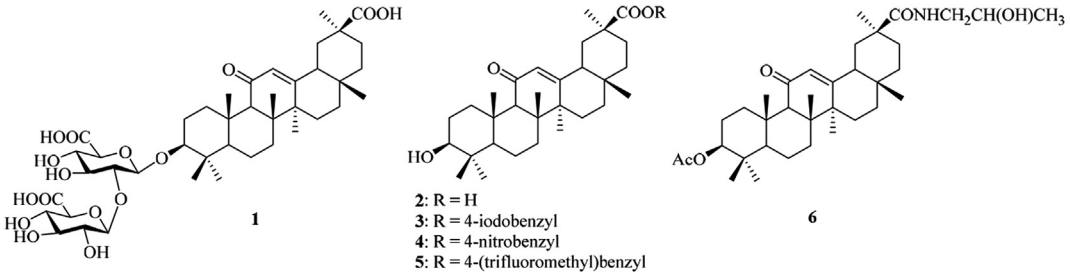


Fig. 1. Chemical structures of glycyrrhizic acid (**1**), GA (**2**) and its semi-synthetic derivatives (**3**–**6**) with antiviral activity.

attention in recent years. Lin et al. have claimed that compound **2** is 7.5-fold more active against EBV ($EC_{50} = 4\ \mu M$) than its parent compound **1** ($EC_{50} = 30\ \mu M$) [11]. Compound **2** shows significant antiviral activity against rotavirus replication at a step or steps subsequent to virus entry [12]. The semi-synthetic derivatives of **2**, such as 4-iodobenzyl ester (**3**), 4-nitrobenzyl ester (**4**) and 4-(trifluoromethyl) benzyl ester (**5**), show potent inhibitory effects on HBV DNA replication activity with IC_{50} s at the micromolar level [13]. A recent study has indicated that GA derivative (**6**), with a 2-hydroxypropyl group at C-30 and an acetyl group at C-3, show remarkable antiviral activity against TK^+ and TK^- strains of HSV-1 with EC_{50} of 4.95 μM [14]. Despite the recognized pharmacological roles as antiviral agents, the main disadvantage of compound **2** and its derivative for application in the food or pharmaceutical industry is their low aqueous solubility due to its non-polar structure (log*P*: 6.75 [15]). It has reported that the solubility of compound **2** in water is only 10.6 μg/mL (37 °C), and the water/n-BuOH partition coefficient is 1.02×10^{-2} (37 °C) [16]. This combination of strong lipophilicity, low solubility and partition coefficient indicates its low bioavailability.

Some strategies have been assessed to overcome the limitation. Cyclodextrins (CDs) are a class of highly water-soluble and biocompatible cyclic oligosaccharides, which can reversely form host-guest inclusion complexes with a variety of guest molecules (drugs), thus improving certain properties of drugs, such as solubility, stability and bioavailability [17,18]. The CD-triterpene inclusion complexes have been also synthesized to increase the aqueous solubility of certain pentacyclic triterpenes [19–21]. Ishida et al. have reported that the complex of compound **2** and HP-γ-CD can improve the oral bioavailability and reduce mRNA expressions of TNF-α, IL-1β and IL-6 [22]. However, such a non-covalent complex is disadvantageous when drug targeting is to be attempted because the complex dissociates before it reaches the organs or tissues to which it is to be delivered [23]. Therefore, direct covalent linkage with β-CD has been suggested, which has been widely used in other water insoluble bioactive molecules, such as fullerene (C_{60}), 5-FU, folic acid and artesunate [24–27]. In our recent studies, a series of water-soluble triazole-bridged β-CD-pentacyclic triterpene conjugates have been synthesized via click chemistry [28,29].

As part of our continued interest in the structurally modified pentacyclic triterpene derivatives as antiviral inhibitors [29–33], we thought it value to prepare a wide range of pentacyclic triterpene derivatives to better explore their antiviral structure-activity relationship (SAR). Herein, we reported the synthesis and anti-influenza A/WSN/33 virus activity of a series of 1:1 β-CD-GA conjugates, in which GA (**2**) was covalently coupled to the primary face of β-CD via C-3 hydroxyl or C-30 carboxylic acid.

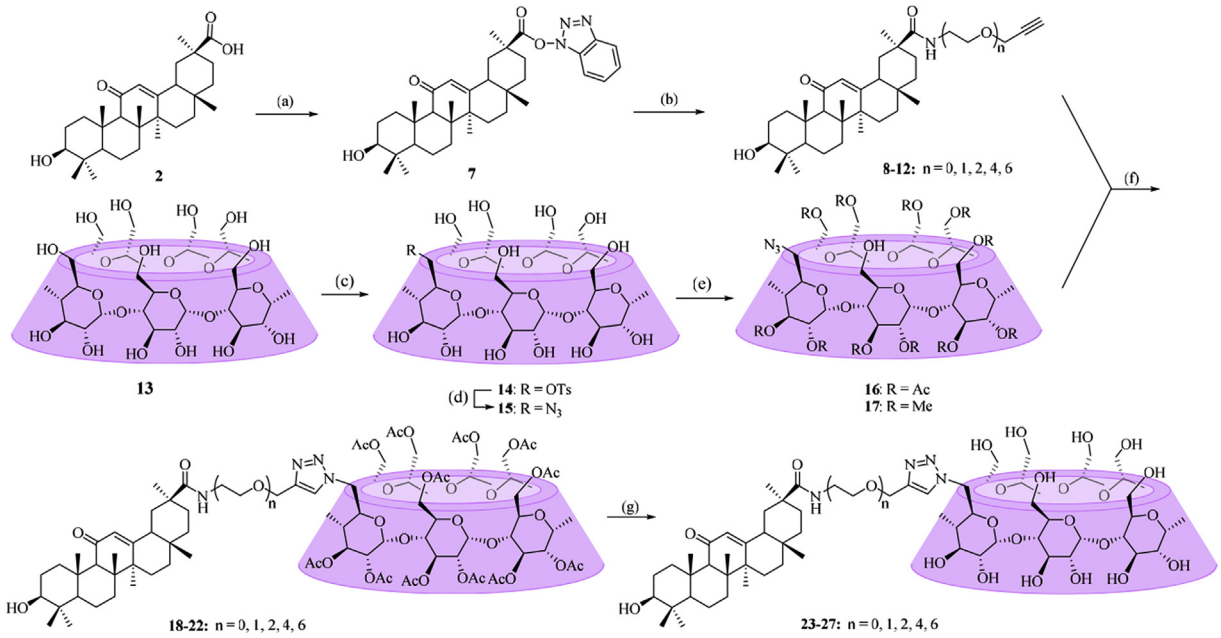
2. Results and discussion

2.1. Chemistry

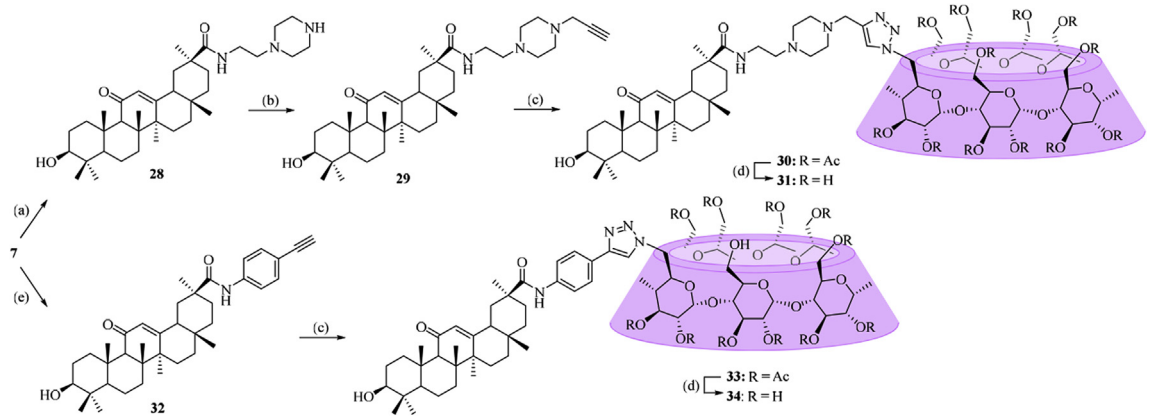
Scheme 1 illustrates the synthesis of β-CD-GA conjugates **23**–**27**. The commercially available GA (**2**) was reacted with 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) in THF to give the stable intermediate **7** in good yield, which proceeded towards a coupling reaction with different terminal alkynyl-functionalized primary amines under basic condition to install a flexible oligo (ethylene glycol) linker (**8**–**12**) in 46–82% yield. Then, **8**–**12** underwent a "click chemistry" reaction with 6^A-azide-6^A-deoxy-per-*O*-acetylated β-CD (**16**), which was prepared from the known β-CD (**13**) in three steps using the conventional method as previously described [34], in THF/H_2O in the presence of a catalytic amount of copper sulfate and sodium ascorbate as reducing agent to yield **18**–**22** with yields ranging from 45% to 61%. At last, the acetyl groups of conjugates **18**–**22** were removed under Zemblén conditions [35] to afford **23**–**27** in 80–98% yields.

To increase the rigidness of the linker, the benzene and piperazine ring were introduced, and Scheme 2 describes the synthesis route for conjugates **30**–**31** and **33**–**34**. The intermediate **7** was reacted either with an excess of 1-(2-aminoethyl) piperazine, followed by *N*-alkylation with propargyl bromide or with an excess of 4-ethynylaniline to give alkynyl-functionalized amides **29** and **32** in moderate yields. Similarly, coupling of compounds **29** and **32** with azide-functionalized per-*O*-acetylated β-CD (**16**) was performed via click reaction, followed by de-*O*-acetylation under Zemplén conditions to give the corresponding conjugates **31** and **34** as the final products.

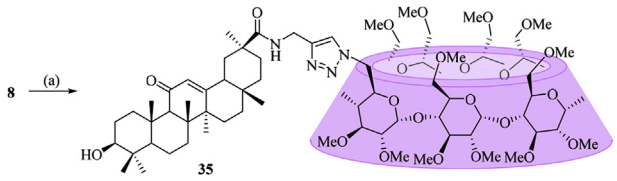
Unlike the β-CD-GA conjugates described above, two other conjugates (**35** and **40**), in which the per-*O*-methylated-β-CD was linked to the carboxylic acid at C-30 of GA or β-CD was linked to the hydroxyl at C-3 of GA, were designed. The method used to prepare conjugate **35** was outlined in Scheme 3, and intermediate **8** was coupled with 6^A-azide-6^A-deoxy-per-*O*-methylated-β-CD (**17**) via click chemistry to furnish conjugate **35**. Conjugate **40** was synthesized according to the procedure described in Scheme 4. In order to synthesize C-3 alkynyl-functionalized compound **37** required for click reaction, the carboxylic acid group at C-30 of GA (**2**) was first protected by treatment with benzyl bromide in DMF, followed by *O*-alkylation at C-3 with propargyl bromide in the presence of sodium hydride. Coupling of compound **16** with *O*-propargyl GA derivative **37** was carried out via click reaction, followed by de-*O*-benzylation and de-*O*-acetylation reactions to give the conjugate **40** in 41% yield over three steps.



Scheme 1. Reagents and conditions: (a) TBTU, DIPEA, THF, 90%; (b) Na_2CO_3, R–NH_2, DMF, 60 °C, 46–82%; (c) TsCl, NaOH, H_2O, 11%; (d) NaN_3, DMF, 80 °C, 81%; (e) Ac_2O, pyridine, DMAP, 86% for **16**, or NaH, CH_3I, DMF, 62% for **17**; (f) sodium L-ascorbate, $CuSO_4$, THF-H_2O (1:1, v/v), 45–61%; (g) CH_3ONa/CH_3OH, 80–98%.



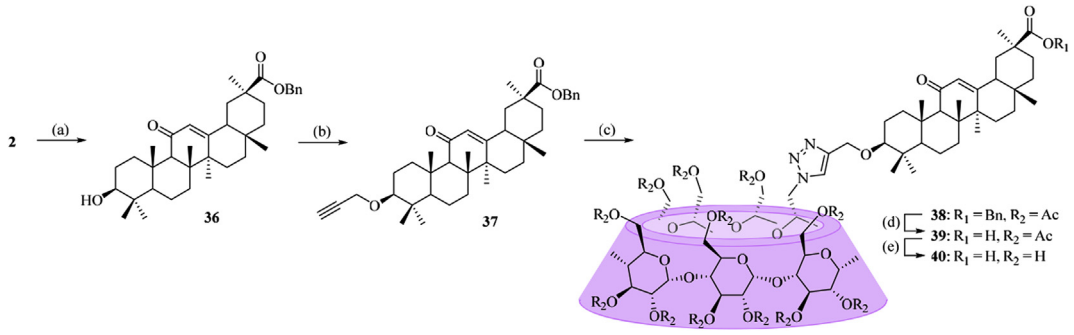
Scheme 2. Reagents and conditions: (a) 2-(piperazin-1-yl)ethan-1-amine, Na_2CO_3, DMF, 60 °C, 45%; (b) propargyl bromide, Na_2CO_3, DMF, 60 °C, 76%; (c) sodium L-ascorbate, $CuSO_4$, THF-H_2O (1:1, v/v), 42% for **30**, 59% for **33**; (d) CH_3ONa/CH_3OH, 90% for **31**, 86% for **34**; (e) 4-ethynylaniline, Na_2CO_3, DMF, 60 °C, 60%.



Scheme 3. Reagents and conditions: (a) sodium L-ascorbate, 6^A-azide-6^A-deoxy-per-*O*-methy-β-CD (**17**), $CuSO_4$, THF-H_2O (1:1, v/v), 59%.

2.2. The calculated ALogP

The logarithm of the *n*-octanol/water partition coefficient (log*P*) is a well-known measure of molecular lipophilicity [36]. It is used to provide invaluable information for the overall understanding of the uptake, distribution, biotransformation and elimination of a wide variety of chemicals. In our study, the calculated Alog*P* values were determined using Pipeline Pilot software, Vers. 7.5 (Accelrys Corporation, San Diego, USA) [37]. Due to the introduction of β-CD along with different linkers, all the conjugates showed increased hydrophilicity compared with their parent compound GA (**2**) (Table 1). A decreased ALog*P* in the order GA (**2**) » per-*O*-alkyl-β-CD-GA conjugates (**18**–**22**, **30**, **33**, **35** and **38**–**39**) » β-CD-GA conjugates (**23**–**27**, **31**, **34** and **40**) was observed. Benefited from the per-*O*-alkyl β-CD moiety, the Alog*P* value was decreased about ~2 units compared with GA (**2**). β-CD-GA conjugates showed the lowest ALog*P* values within the range of 0.09–0.77, indicating that their solubility in water was about 47,000-fold higher than their parent compound GA (**2**). As a matter of fact, during the biological assays of the prepared β-CD-GA conjugates, the parent compound GA (**2**) dissolved in water formed turbid solutions at a concentration of 50 μM and suspensions accompanied by a precipitate even when 5% DMSO (v/v) solutions were used. However, all the β-CD-GA conjugates exhibited greater water solubility generating clear solutions at the same concentration when 1% DMSO (v/v) solutions were used.



Scheme 4. Reagents and conditions: (a) benzyl bromide, K_2CO_3, DMF, 50 °C, 80%; (b) NaH, propargyl bromide, THF, 65 °C, 60%; (c) sodium L-ascorbate, 6^A-azide-6^A-deoxy-per-*O*-acetylated-β-CD (**16**), $CuSO_4$, THF-H_2O (1:1, v/v), 60%; (d) Pt/C, H_2, CH_3OH, 76%; (e) CH_3ONa/CH_3OH, 81%.

Table 1
Calculated AlogP values of conjugates[a].

Compd	AlogP	Compd	AlogP	Compd	AlogP
GA (**2**)	5.45	**24**	0.11	**34**	0.77
18	3.55	**25**	0.10	**35**	3.28
19	3.63	**26**	0.15	**38**	4.07
20	3.66	**27**	0.26	**39**	3.58
21	3.61	**30**	3.50	**40**	0.34
22	3.61	**31**	0.12		
23	0.09	**33**	3.99		

[a] AlogP values (Ghose and Crippen octanol-water partition coefficient at 25 °C) were calculated using Pipeline Pilot software, version 7.5 (Accelrys Corp., San Diego, CA, USA).

2.3. In vitro cytotoxic activity

The *in vitro* cytotoxic activity was evaluated for all of the synthesized conjugates **18**–**27**, **30**–**31**, **33**–**35** and **38**–**40** using CellTiter-Glo® Assay. The results showed that most conjugates had no cytotoxicity against uninfected Madin-Daby canine kidney (MDCK) cells at a concentration of 50 μM, except for compound **35** possessing cytotoxicity at the same concentration (Fig. 2). This finding, together with our previous observation that per-*O*-methylated-β-CD derivatives of other pentacyclic triterpenes show different cytotoxicity at a concentration of 5–50 μM [28], indicated that per-*O*-methylated-β-CD might impart certain degree of cytotoxicity *in vitro*.

2.4. Anti-influenza virus activity of β-CD-GA conjugates

Except for compound **35** with certain cytotoxic activity as described above, the other 17 β-CD-GA conjugates were evaluated against the influenza virus A/WSN/33 (H1N1) that was propagated in MDCK cells at one concentration (50 μM) by the cytopathic effect (CPE) reduction assay. Oseltamivir (OSV) and DMSO were used as positive and negative controls, respectively. Fig. 3 lists the primarily screen results.

The five conjugates (**23**–**27**) with the GA and β-CD groups held constant, but with varying of the oligoethylene glycol linker revealed that compound **25** had the highest antiviral activity to A/WSN/33 (H1N1) virus, indicating 1,2,3-triazole moiety along with diethylene glycol linker could allow a better fit between GA and the proper target. Elongation or shortening of the diethylene glycol chain leads to some decrease of the antiviral activity. Similar results were also observed for conjugates **18**–**22**, in which the β-CD was acetylated, and compound **20** showed the greatest antiviral activity. The diethylene glycol linker of compounds **20** and **25** was further modified by replacing one ethylene glycol moiety with piperazine ring to increase the rigidness of the linker, leading to greatly reduced activity (**20** *vs.* **30**, **25** *vs.* **31**). However, the introduction of an aromatic linker (1,2,3-triazol-4-yl)phenyl between β-CD and GA still retained reasonable antiviral activity (**23** *vs.* **34**). To our surprise, the introduction of aromatic amino acids methyl esters at C-30 of glycyrrhizin also showed more potent anti-influenza activity

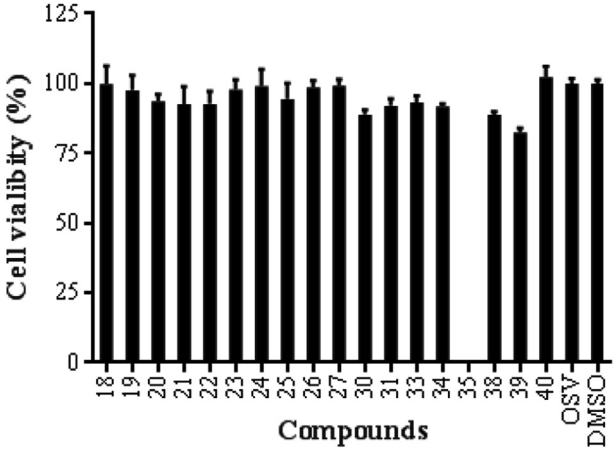


Fig. 2. The *in vitro* cytotoxic screening of β-CD-GA conjugates **18**–**27**, **30**–**31**, **33**–**35** and **38**–**40** against MDCK cells using CellTiter-Glo® Assay.

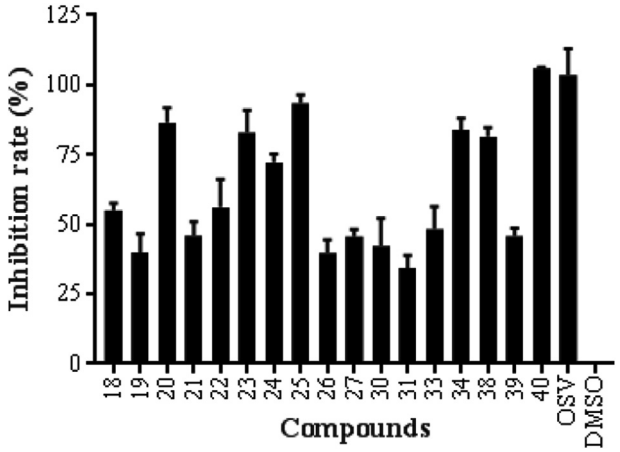


Fig. 3. The CPE-based screen of β-CD-GA conjugates (50 μM). MDCK was utilized as the host cells to test A/WSN/33 virus infection; OSV and DMSO acted as positive and negative control, respectively. Error bars indicate standard deviations of triplicate experiments.

than their parent compound [9], indicating an aromatic group at C-30 might be helpful for the binding of GA with its receptor. Evaluation of the three derivatives (**18**, **23** and **35**) with the same linker of (1,2,3-triazol-4-yl)methyl at the C-30 of GA revealed that the substitution of β-CD showed important effect on the activity and cytotoxicity. The *O*-acetylation of β-CD reduced the activity (**18** *vs.* **23**), while the *O*-methylation of β-CD only resulted in the cytotoxicity (**18** and **23** *vs.* **35**). The carboxylic acid derivative **40**, shift of the β-CD moiety from C-30 to C-3, had the highest antiviral activity of the new compounds reported in this study, indicating that the C-3 hydroxy of GA was tolerated. Compared with the weak anti-influenza A/H1N1/pdm09 virus activity of glycyrrhizin (**1**) (EC_{50} = 364.6 μM) [9], the effect of β-CD on the antiviral activity of GA is obviously more potent than that of two molecules of glucuronic acid.

3. Conclusions

In summary, a series of GA derivatives, altered at position C-3 hydroxy or C-30 carboxylic acid by attachment of β-CD with different linkers, were designed, synthesized and evaluated for their anti-influenza virus activity. The solubility of these β-CD-GA conjugates in water was much higher than their parent compound as deduced from the calculated Alog*P* values. Our current investigation indicated that the conjugation of per-*O*-methylated β-CD to GA displayed certain cytotoxicity toward MDCK cells. Six β-CD-GA conjugates showed promising antiviral activity for A/WSN/33 (H1N1) virus, while no cytotoxicity was observed. This study supported that these conjugates were potential candidates of anti-influenza virus agents.

4. Experimental

4.1. Chemistry

4.1.1. General information

High resolution mass spectra (ESI-HRMS) were obtained with a Thermo Scientific Q Exactive spectrometer (Bremen, Germany) in the positive ESI mode. NMR spectra were recorded on a Bruker DRX 400 or DRX 600 spectrometer at ambient temperature. ^{1}H NMR chemical shifts were referenced to the internal standard TMS (δ_H = 0.00) or the solvent signal (δ_H = 3.31 for the central line of MeOD). ^{13}C NMR chemical shifts were referenced to the solvent signal (δ_C = 77.00 for the central line of $CDCl_3$, δ_C = 49.00 for the central line of MeOD). Reactions were monitored by thin-layer chromatography (TLC) on a pre-coated silica gel 60 F_{254} plate (layer thickness of 0.2 mm; E. Merck, Darmstadt, Germany) and detected by staining with a yellow solution containing Ce(NH_4)$_2$(NO_3)$_6$ (0.5 g) and (NH_4)$_6$$Mo_7O_{24}4H_2O$ (24.0 g) in 6% H_2SO_4 (500 mL), followed by heating. Flash column chromatography was performed on silica gel 60 (200–300 mesh, Qingdao Haiyang Chemical Co., Ltd.).

The syntheses of **7**, **8**, **14**–**17** and **36** was performed as previously reported [34,38–40].

4.1.2. General procedure A for the click reaction

To a solution of alkyne (0.10 mmol) and azide (0.10 mmol) in 1:1 THF-H_2O (5 mL), $CuSO_4$ (15.7 mg, 0.10 mmol) and sodium L-ascorbate (40.9 mg, 0.20 mmol) were added. The resulting solution was vigorously stirred for 12 h at room temperature. The reaction mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organics were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography.

4.1.3. General procedure B for the deacetylation reaction

The per-*O*-acetylated-β-CD-GA conjugate was dissolved in dry methanol (~5 mL per 100 mg of compound), and a solution of sodium methoxide (30% in methanol, 0.1 eq per mol of acetate) was added. The solution was stirred at room temperature for 4–6 h. After completion (TLC), the reaction mixture was neutralized with Amberlite IR-120 (H^+) ion exchange resin, filtered and concentrated. The crude product was purified by RP column chromatography (eluted by CH_3OH).

4.1.4. General procedure C for the amidation reaction

To a solution of compound **7** (200 mg, 0.34 mmol) and terminal alkynyl substituted amine (0.43 mmol) in DMF (10 mL), Na_2CO_3 (72 mg, 0.68 mmol) was added. The resulting solution was vigorously stirred for 24 h at 60 °C. The solvent was removed by steaming. The residue was purified by column chromatography.

4.1.5. Synthesis of N-(2-(2-propyn-1-yloxy)ethyl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (*9*)

Prepared from **7** and 2-(propyn-1-yloxy)-ethanamine according to general procedure C, the residue was purified by flash chromatography (eluent: petroleum ether:acetone = 4:1) to afford **9** as a white solid with a yield of 46%. R_f = 0.70 (petroleum ether:-acetone = 1:1); m.p. 212–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (br s, 1H), 5.62 (s, 1H), 4.17 (d, 2H, *J* = 2.3 Hz), 3.61–3.39 (m, 4H), 3.20 (dd, 1H, *J* = 10.7, 5.5 Hz), 2.76 (td, 1H, *J* = 10.2, 3.1 Hz), 2.48 (t, 1H, *J* = 2.4 Hz), 2.31 (s, 1H), 2.17–1.02 (m, other aliphatic ring protons), 1.35 (s, 3H, CH_3), 1.11 (s, 6H, 2 × CH_3), 1.10, 0.98, (s, each 3H, 2 × CH_3), 0.92 (dd, 1H, *J* = 12.9, 4.3 Hz), 0.79, 0.78 (s, each 3H, 2 × CH_3), 0.67 (d, 1H, *J* = 11.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.03, 175.79, 169.08, 128.47, 79.36, 78.73, 77.05, 75.13, 68.69, 61.83, 58.28, 54.97, 48.07, 45.37, 43.62, 43.18, 41.90, 39.23, 39.14, 39.11, 37.47, 37.07, 32.77, 31.90, 31.44, 29.50, 28.51, 28.12, 27.27, 26.50, 26.41, 23.36, 18.66, 17.48, 16.36, 15.59; ESI-HRMS (*m*/*z*) Calcd for $C_{35}H_{53}NO_4$ [M + H]$^+$: 552.4047. Found 552.4041.

4.1.6. Synthesis of N-(2-(2-(2-propyn-1-yloxy)ethoxy)ethyl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (*10*)

Prepared from **7** and 2-(2-(2-propyn-1-yloxy)ethoxy)-ethanamine according to general procedure C, the residue was purified by flash chromatography (eluent: petroleum ether:acetone = 3:1) to afford **10** as a white solid with a yield of 82%. R_f = 0.55 (petroleum ether:acetone = 1:1); m.p. 141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.22 (br s, 1H), 5.65 (s, 1H), 4.16 (d, 2H, *J* = 2.9 Hz), 3.69–3.39 (m, 8H), 3.19 (dd, 1H, *J* = 10.7, 5.4 Hz), 2.75 (td, 1H, *J* = 10.4, 3.4 Hz), 2.41 (t, 1H, *J* = 2.2 Hz), 2.30 (s, 1H), 2.14 (dd, 1H, *J* = 13.2, 3.3 Hz), 2.06–1.55 (m, 10H), 1.42–1.01 (m, other aliphatic ring protons), 1.35 (s, 3H, CH_3), 1.10 (s, 9H, 3 × CH_3), 0.97 (s, 3H, CH_3), 0.91 (dd, 1H, *J* = 12.8, 3.9 Hz), 0.78 (2 × s, each 3H, 2 × CH_3), 0.66 (d, 1H, *J* = 11.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.98, 175.71, 169.17, 128.29, 79.44, 78.56, 74.63, 69.88, 69.83, 68.91, 61.69, 58.24, 54.82, 47.96, 45.24, 43.48, 43.04, 41.62, 39.10, 39.03, 38.87, 37.34, 36.90, 32.61, 31.75, 31.31, 29.39, 28.43, 28.02, 27.11, 26.34, 26.26, 23.27, 18.52, 17.35, 16.27, 15.53; ESI-HRMS (*m*/*z*) Calcd for $C_{37}H_{57}NO_5$ [M + H]$^+$: 596.4310. Found 596.4300.

4.1.7. Synthesis of N-(3,6,9,12-tetraoxapentadec-14-yn-1-yl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (*11*)

Prepared from **7** to 3,6,9,12-tetraoxapentadec-14-yn-1-amine according to general procedure C, the residue was purified by flash chromatography (eluent: DCM: MeOH = 20:1) to afford **11** as a white solid with a yield of 52%. R_f = 0.40 (eluent: DCM:MeOH = 10:1); m.p. 52–54 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.22 (t, 1H, *J* = 5.5 Hz), 5.67 (s, 1H), 4.19 (d, 2H, *J* = 2.4 Hz), 3.71–3.61 (m, 12H), 3.57–3.54 (m, 2H), 3.52–3.39 (m, 2H), 3.22 (dd,

1H, $J = 10.6$, 5.6 Hz), 2.78 (td, 1H, $J = 10.2$, 3.4 Hz), 2.43 (d, 1H, $J = 2.4$ Hz), 2.32 (s, 1H), 2.19–2.15 (m, 1H), 2.07–2.00 (m, 1H), 1.95–1.92 (m, 1H), 1.87–0.99 (m, other aliphatic ring protons), 1.37 (s, 3H, CH_3), 1.12 (s, 9H, $3 \times CH_3$), 1.00 (s, 3H, CH_3), 0.80 ($2 \times$ s, 6H, $2 \times CH_3$), 0.69 (d, 1H, $J = 11.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.94, 175.74, 169.11, 128.47, 79.59, 78.76, 74.56, 70.58, 70.50, 70.46, 70.37, 70.21, 70.02, 69.09, 61.82, 58.39, 54.95, 48.03, 45.34, 43.57, 43.19, 41.87, 39.16, 39.13, 37.49, 37.07, 32.77, 31.86, 31.48, 29.46, 28.53, 28.09, 27.29, 26.49, 26.43, 23.38, 18.67, 17.48, 16.35, 15.56; ESI-HRMS (m/z) Calcd for $C_{41}H_{65}NO_7$ $[M + NH_4]^+$: 701.5099. Found 701.5090.

4.1.8. Synthesis of N-(3,6,9,12,15,18-hexaoxaheneicos-20-yn-1-yl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**12**)

Prepared from **7** to 3,6,9,12,15,18-hexaoxaheneicos-20-yn-1-amine according to general procedure C, the residue was purified by flash chromatography (eluent: petroleum ether:acetone = 4:1) to afford **12** as a yellow oil with a yield of 52%. $R_f = 0.35$ (petroleum ether:acetone = 1:1); ^1H NMR (400 MHz, $CDCl_3$): δ 6.30 (t, 1H, $J = 5.5$ Hz), 5.64 (s, 1H), 4.17–4.16 (m, 2H), 3.67–3.40 (m, 25H), 3.18 (dd, 1H, $J = 10.8$, 4.7 Hz), 2.74 (td, 1H, $J = 10.4$, 2.6 Hz), 2.41 (d, 1H, $J = 2.4$ Hz), 2.29 (s, 1H), 2.15–0.88 (m, other aliphatic ring protons), 1.34 (s, 3H, CH_3), 1.09 (s, 9H, $3 \times CH_3$), 0.97 (s, 3H, CH_3),0.77 (s, 6H, $2 \times CH_3$), 0.64 (d, 1H, $J = 11.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.84, 175.71, 169.05, 128.35, 79.57, 78.60, 74.49, 70.48, 70.46, 70.44, 70.37, 70.29, 70.10, 69.98, 68.99, 61.73, 58.29, 54.89, 47.96, 45.26, 43.47, 43.10, 41.73, 39.14, 39.04, 37.41, 36.98, 32.69, 31.77, 31.37, 29.35, 28.45, 28.04, 27.18, 26.41, 26.35, 23.29, 18.58, 17.40, 16.26, 15.52; ESI-HRMS (m/z) Calcd for $C_{45}H_{73}NO_9$ $[M + NH_4]^+$: 789.5624. Found 789.5611.

4.1.9. Synthesis of N-(1-(6^A-deoxy-per-O-acetylated-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)methyl-3β-hydroxy-11-oxo-olean-12-en-30-amide (**18**)

Prepared from **8** and **16** according to general procedure A, the residue was purified by flash chromatography (eluent: petroleum ether:acetone = 1:1) to afford **18** as a white foam with a yield of 52%. $R_f = 0.12$ (petroleum ether:acetone = 1:1); ^1H NMR (600 MHz, $CDCl_3$): δ 7.51 (s, 1H), 6.64 (t, 1H, $J = 5.2$ Hz), 5.61 (s, 1H), 5.46 (d, 1H, $J = 3.9$ Hz), 5.35–5.16 (m, 7H), 5.15 (d, 1H, $J = 3.5$ Hz), 5.11 (d, 1H, $J = 4.0$ Hz), 5.08 (d, 1H, $J = 4.0$ Hz), 5.04 (t, 2H, $J = 4.1$ Hz), 4.99 (d, 1H, $J = 3.4$ Hz), 4.93–4.72 (m, 8H), 4.66 (d, 1H, $J = 11.7$ Hz), 4.62 (dd, 1H, $J = 15.4$, 6.1Hz), 4.57–4.51 (m, 5H), 4.46 (dd, 1H, $J = 15.3$, 4.9 Hz), 4.34–4.08 (m, 13H), 3.98 (d, 1H, $J = 9.1$ Hz), 3.87 (dd, 1H, $J = 12.4$, 3.4 Hz), 3.74–3.68 (m, 5H), 3.63 (t, 1H, $J = 8.8$ Hz), 3.53 (t, 1H, $J = 9.1$ Hz), 3.20 (d, 1H, $J = 10.3$ Hz), 2.74 (td, 1H, $J = 10.4$, 3.3 Hz), 2.29 (s, 1H), 2.19–1.80 (m, 75H), 1.68–1.56 (m, 5H), 1.44–0.91 (m, other aliphatic ring protons), 1.35 (s, 3H, CH_3), 1.10 (s, 9H, $3 \times CH_3$), 0.98, 0.79, 0.78 (s, each 3H, $3 \times CH_3$), 0.67 (d, 1H, $J = 11.6$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$): 199.84, 175.94, 170.84, 170.79, 170.72, 170.65, 170.60, 170.59, 170.57, 170.53, 170.51, 170.39, 170.36, 170.25, 169.50, 169.44, 169.39, 169.35, 169.32, 169.30, 169.19, 168.95, 144.82, 128.43, 124.48, 97.11, 96.91, 96.89, 96.82, 96.79, 96.57, 96.40, 78.70, 78.25, 77.12, 77.03, 76.94, 76.56, 76.47, 75.92, 71.68, 71.27, 71.19, 71.01, 70.76, 70.61, 70.33, 70.23, 70.17, 70.05, 69.92, 69.86, 69.71, 69.64, 69.48, 69.29, 69.27, 62.79, 62.75, 62.61, 62.46, 62.33, 62.17, 61.73, 54.88, 49.74, 48.01, 45.26, 43.49, 43.15, 41.43, 39.11, 39.07, 37.44, 37.01, 35.04, 32.73, 31.85, 31.37, 29.32, 28.44, 28.05, 27.21, 26.44, 26.39, 23.32, 20.90, 20.77, 20.74, 20.72, 20.70, 20.66, 20.62, 18.66, 17.45, 16.30, 15.53; ESI-HRMS (m/z) Calcd for $C_{115}H_{159}N_4O_{57}$ $[M + H]^+$: 2507.9661. Found 2507.9614.

4.1.10. Synthesis of N-(2-((1-(6^A-deoxy-per-O-acetylated-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)methoxy)ethyl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**19**)

Prepared from **9** and **16** according to general procedure A, the residue was purified by flash chromatography (eluent: petroleum ether:acetone = 1:1) to afford **19** as a white foam with a yield of 60%. $R_f = 0.20$ (petroleum ether:acetone = 1:1); ^1H NMR (600 MHz, $CDCl_3$): δ 7.69 (s, 1H), 6.26 (t, 1H, $J = 5.3$ Hz), 5.63 (s, 1H), 5.59 (d, 1H, $J = 3.8$ Hz), 5.35–5.16 (m, 9H), 5.09 (d, 1H, $J = 4.1$ Hz), 5.07 (d, 1H, $J = 4.0$ Hz), 5.04 (d, 1H, $J = 3.6$ Hz), 5.03 (d, 1H, $J = 3.7$ Hz), 4.98 (d, 1H, $J = 3.5$ Hz), 4.92 (dd, 1H, $J = 8.6$, 4.0 Hz), 4.83–4.79 (m, 3H), 4.73 (dd, 1H, $J = 9.8$, 3.6 Hz), 4.67–4.51 (m, 9H), 4.47 (dd, 1H, $J = 10.4$, 3.5 Hz), 4.43 (d, 1H, $J = 11.5$ Hz), 4.30–4.05 (m, 14H), 3.77–3.42 (m, 11H), 3.18 (dd, 1H, $J = 11.3$, 4.8 Hz), 2.74 (td, 1H, $J = 10.3$, 3.4 Hz), 2.30 (s, 1H), 2.17–1.93 (m, 75H), 1.81–1.00 (m, other aliphatic ring protons), 1.34, 1.10 (s, each 3H, $2 \times CH_3$), 1.09 (s, 6H, $2 \times CH_3$), 0.97 (s, 3H, CH_3), 0.92 (dd, 1H, $J = 13.4$, 3.2 Hz), 0.78, 0.77 (s, each 3H, $2 \times CH_3$), 0.66 (d, 1H, $J = 11.3$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.92, 175.73, 170.80, 170.69, 170.66, 170.63, 170.59, 170.52, 170.45, 170.43, 170.35, 170.31, 170.22, 170.19, 169.50, 169.33, 169.31, 169.25, 169.22, 169.18, 169.11, 144.31, 128.33, 125.67, 97.02, 96.89, 96.72, 96.66, 96.55, 96.52, 96.31, 78.55, 77.34, 76.95, 76.81, 76.57, 76.50, 75.65, 71.54, 71.36, 71.26, 70.92, 70.86, 70.36, 70.29, 70.11, 69.97, 69.90, 69.82, 69.71, 69.59, 69.55, 69.52, 69.40, 69.22, 64.18, 62.67, 62.61, 62.53, 62.34, 62.15, 61.72, 54.87, 49.21, 47.97, 45.26, 43.50, 43.12, 41.74, 39.14, 39.11, 39.05, 37.41, 37.02, 32.69, 31.77, 31.41, 29.33, 28.48, 28.03, 27.21, 26.42, 26.36, 20.79, 20.77, 20.75, 20.72, 20.69, 20.67, 20.64, 20.59, 20.56, 18.62, 17.41, 16.30, 15.52; ESI-HRMS (m/z) Calcd for $C_{117}H_{162}N_4O_{58}$ $[M + H]^+$: 2551.9923. Found 2551.9897.

4.1.11. Synthesis of N-(2-(2-((1-(6^A-deoxy-per-O-acetylated-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)methoxy)ethoxy)ethyl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**20**)

Prepared from **10** and **16** according to general procedure A, the residue was purified by flash chromatography (eluent: petroleum ether: acetone = 1:1) to afford **20** as a white foam with a yield of 50%. $R_f = 0.30$ (petroleum ether:acetone = 1:1); ^1H NMR (600 MHz, $CDCl_3$): δ 7.64 (s, 1H), 6.19 (t, 1H, $J = 5.4$ Hz), 5.67 (s, 1H), 5.63 (d, 1H, $J = 3.8$ Hz), 5.37–5.17 (m, 9H), 5.12 (d, 1H, $J = 4.1$ Hz), 5.09 (d, 1H, $J = 4.0$ Hz), 5.06 (d, 1H, $J = 3.6$ Hz), 5.04 (d, 1H, $J = 3.7$ Hz), 5.00 (d, 1H, $J = 3.5$ Hz), 4.93 (dd, 1H, $J = 8.6$, 4.0 Hz), 4.84–4.81 (m, 3H), 4.76–4.73 (m, 2H), 4.69–4.66 (m, 3H), 4.62 (dd, 1H, $J = 15.0$, 4.4 Hz), 4.58–4.46 (m, 6H), 4.31–4.06 (m, 14H), 3.77–3.40 (m, 15H), 3.20 (dd, 1H, $J = 11.3$, 4.9 Hz), 2.76 (td, 1H, $J = 10.2$, 3.3 Hz), 2.32 (s, 1H), 2.16–2.00 (m, 73H), 1.92–1.57 (m, 12H), 1.43–1.01 (m, other aliphatic ring protons), 1.36, 1.11 (s, each 3H, $2 \times CH_3$), 1.10 (s, 6H, $2 \times CH_3$), 0.99 (s, 3H, CH_3), 0.94 (dd, 1H, $J = 13.2$, 3.9 Hz), 0.79 ($2 \times$ s, each 3H, $2 \times CH_3$), 0.68 (d, 1H, $J = 11.3$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.93, 175.73, 170.84, 170.73, 170.69, 170.63, 170.57, 170.55, 170.49, 170.38, 170.35, 170.26, 170.24, 169.58, 169.40, 169.36, 169.29, 169.26, 169.16, 169.11, 144.53, 128.43, 125.68, 97.05, 97.01, 96.76, 96.65, 96.53, 96.38, 78.66, 77.02, 76.79, 76.59, 76.47, 75.73, 71.57, 71.39, 71.29, 70.99, 70.89, 70.46, 70.40, 70.32, 70.19, 70.14, 70.00, 69.96, 69.85, 69.65, 69.63, 69.55, 69.51, 69.46, 69.26, 64.39, 62.73, 62.62, 62.56, 62.42, 62.19, 61.77, 54.91, 49.16, 47.99, 45.30, 43.54, 43.16, 41.79, 39.11, 39.08, 37.45, 37.04, 32.74, 31.84, 31.46, 30.87, 29.41, 28.50, 28.06, 27.27, 26.46, 26.40, 23.33, 20.82, 20.80, 20.79, 20.76, 20.73, 20.71, 20.69, 20.67, 20.62, 20.59, 18.65, 17.45, 16.33, 15.55; ESI-HRMS (m/z) Calcd for $C_{119}H_{166}N_4O_{59}$ $[M + H]^+$: 2596.0185. Found 2596.0154.

*4.1.12. Synthesis of N-(1-(1-(6^A-deoxy-per-O-acetylated-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)-2,5,8,11-tetraoxatridecan-13-yl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**21**)*

Prepared from **11** and **16** according to general procedure A, the residue was purified by flash chromatography (eluent: petroleum ether: acetone = 1:1) to afford **21** as a white foam with a yield of 61%. R_f = 0.70 (petroleum ether:acetone = 1:2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (s, 1H), 6.16 (t, 1H, *J* = 5.2 Hz), 5.66 (s, 1H), 5.64 (d, 1H, *J* = 3.8 Hz), 5.36–5.25 (m, 7H), 5.18–5.16 (m, 2H), 5.12 (d, 1H, *J* = 4.1 Hz), 5.09 (d, 1H, *J* = 4.0 Hz), 5.06 (d, 1H, *J* = 3.6 Hz), 5.04 (d, 1H, *J* = 3.7 Hz), 5.01 (d, 1H, *J* = 3.6 Hz), 4.94 (dd, 1H, *J* = 8.6, 4.0 Hz), 4.84–4.81 (m, 3H), 4.75 (dd, 2H, *J* = 9.3, 3.4 Hz), 4.69–4.65 (m, 3H), 4.61 (dd, 1H, *J* = 15.6, 3.1 Hz), 4.58–4.53 (m, 4H), 4.47–4.19 (m, 2H), 4.30–4.06 (m, 13H), 3.76–3.46 (m, 21H), 3.20 (dd, 1H, *J* = 11.3, 4.9 Hz), 2.76 (td, 1H, *J* = 13.4, 3.2 Hz), 2.31 (s, 1H), 2.18–2.01 (m, 62H), 1.92–1.01 (m, other aliphatic ring protons), 1.36 (s, 3H, CH_3), 1.11 (s, 6H, 2 × CH_3), 1.10, 0.99 (s, each 3H, 2 × CH_3), 0.95 (td, 1H, *J* = 16.1, 4.1 Hz), 0.80, 0.79 (s, each 3H, 2 × CH_3), 0.68 (d, 1H, *J* = 11.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.89, 175.68, 170.83, 170.73, 170.69, 170.62, 170.55, 170.49, 170.46, 170.37, 170.35, 170.26, 170.24, 169.59, 169.39, 169.36, 169.28, 169.26, 169.17, 169.06, 144.62, 128.43, 125.64, 97.03, 96.76, 96.64, 96.53, 96.50, 96.38, 78.66, 77.12, 77.04, 76.99, 76.78, 76.58, 76.48, 75.78, 71.58, 71.37, 71.29, 70.98, 70.90, 70.51, 70.45, 70.42, 70.33, 70.18, 70.13, 70.00, 69.95, 69.92, 69.83, 69.66, 69.62, 69.59, 69.53, 69.51, 69.46, 69.45, 69.25, 64.49, 62.75, 62.61, 62.57, 62.52, 62.43, 62.20, 61.78, 54.91, 49.10, 48.00, 45.30, 43.54, 43.15, 41.83, 39.12, 39.09, 39.07, 37.46, 37.04, 32.74, 31.84, 31.46, 29.44, 28.50, 28.06, 27.26, 26.45, 26.40, 23.36, 20.82, 20.79, 20.76, 20.73, 20.70, 20.68, 20.67, 20.62, 20.58, 18.64, 17.45, 16.32, 15.55; ESI-HRMS (*m*/*z*) Calcd for $C_{123}H_{174}N_4O_{61}$ $[M + H]^+$: 2684.0709. Found 2684.0696.

*4.1.13. Synthesis of N-(1-(1-(6^A-deoxy-per-O-acetylated-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)-2,5,8,11,14,17-hexaoxanonadecan-19-yl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**22**)*

Prepared from **12** and **16** according to general procedure C, the residue was purified by flash chromatography (eluent: petroleum ether:acetone = 1:1) to afford **22** as a white foam with a yield of 45%. R_f = 0.10 (petroleum ether:acetone = 1:2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (s, 1H), 6.20 (t, 1H, *J* = 4.8 Hz), 5.66 (s, 1H), 5.65 (d, 1H, *J* = 4.0 Hz), 5.36–5.24 (m, 8H), 5.20–5.16 (m, 2H), 5.12 (d, 1H, *J* = 4.0 Hz), 5.09 (d, 1H, *J* = 4.0 Hz), 5.07 (d, 1H, *J* = 3.6 Hz), 5.05 (d, 1H, *J* = 3.6 Hz), 5.01 (d, 1H, *J* = 3.6 Hz), 4.94 (dd, 1H, *J* = 8.6, 4.0 Hz), 4.85–4.80 (m, 3H), 4.75 (dd, 2H, *J* = 9.7, 3.6 Hz), 4.71–4.46 (m, 10H), 4.31–4.06 (m, 13H), 3.77–3.39 (m, 29H), 3.21 (dd, 1H, *J* = 10.6, 5.3 Hz), 2.77 (td, 1H, *J* = 10.3, 3.3 Hz), 2.32 (s, 1H), 2.20–1.57 (m, 81H), 1.43–1.02 (m, other aliphatic ring protons), 1.36 (s, 3H, CH_3), 1.11 (s, 9H, 3 × CH_3), 0.99 (s, 3H, CH_3), 0.94 (dd, 1H, *J* = 13.6, 4.0 Hz), 0.80, 0.79 (s, each 3H, 2 × CH_3), 0.69 (d, 1H, *J* = 11.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$):δ 199.92, 175.73, 170.84, 170.75, 170.71, 170.64, 170.57, 170.51, 170.47, 170.39, 170.37, 170.28, 170.26, 169.62, 169.41, 169.31, 169.29, 169.21, 169.09, 144.68, 129.51, 128.45, 125.66, 97.05, 96.78, 96.65, 96.55, 96.50, 96.41, 78.69, 77.12, 77.05, 77.00, 76.79, 76.61, 76.47, 75.80, 71.60, 71.37, 71.29, 70.99, 70.91, 70.51, 70.44, 70.35, 70.18, 70.16, 70.03, 69.96, 69.85, 69.70, 69.66, 69.64, 69.58, 69.55, 69.52, 69.48, 69.28, 64.52, 62.76, 62.62, 62.58, 62.52, 62.44, 62.22, 61.80, 54.93, 53.78, 49.12, 48.00, 45.32, 43.55, 43.17, 41.84, 39.14, 39.11, 37.47, 37.05, 32.75, 31.85, 31.70, 31.47, 30.64, 29.24, 28.52, 28.07, 27.27, 26.47, 26.42, 23.37, 20.83, 20.80, 20.77, 20.74, 20.72, 20.70, 20.68, 20.64, 20.60, 18.65, 17.46, 16.33, 15.56; ESI-HRMS (*m*/*z*) Calcd for $C_{127}H_{182}N_4O_{63}$ $[M + H]^+$: 2772.1233. Found 2772.1228.

*4.1.14. Synthesis of N-(1-(6^A-deoxy-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)methyl-3β-hydroxy-11-oxo-olean-12-en-30-amide (**23**)*

Prepared from **18** according to general procedure B, the residue was purified by RP flash chromatography (eluent: methanol) to afford **23** as a white foam with a yield of 86%. ^{1}H NMR (600 MHz, MeOD:$CDCl_3$ = 2:1): δ 7.83 (s, 1H), 5.64 (s, 1H), 5.11 (d, 1H, *J* = 3.0 Hz), 4.99–4.97 (m, 6H), 4.93 (d, 2H, *J* = 2.3 Hz), 4.66–4.59 (m, 1H), 5.48 (s, 1H), 5.09 (t, 1H, *J* = 9.2 Hz), 3.89–3.71 (m, 22H), 3.60–3.40 (m, 15H), 3.19–3.09 (m, 2H), 2.73 (d, 1H, *J* = 13.2 Hz), 2.44 (s, 1H), 2.20–0.89 (m, other aliphatic ring protons), 1.42 (s, 3H, CH_3), 1.14 (s, 9H, 3 × CH_3), 0.99, 0.82, 0.80 (s, each 3H, 3 × CH_3), 0.76 (d, 1H, *J* = 11.6 Hz); ^{13}C NMR (150 MHz, MeOD:$CDCl_3$ = 2:1): δ 201.19, 171.09, 157.03, 145.12, 127.78, 124.72, 102.65, 102.55, 102.47, 102.39, 102.11, 83.59, 81.78, 81.75, 81.7, 81.58, 81.48, 78.11, 78.03, 77.89, 77.67, 73.41, 73.34, 73.25, 73.05, 72.88, 72.84, 72.72, 72.52, 72.50, 72.31, 72.28, 71.89, 70.64, 61.76, 60.45, 60.38, 60.03, 54.82, 50.85, 48.21, 45.32, 43.42, 43.20, 41.18, 39, 38.84, 37.36, 36.94, 34.56, 32.46, 31.56, 30.55, 29.44, 29.34, 29.24, 29.21, 29.07, 28.93, 28.17, 28.10, 27.87, 27.31, 26.44, 26.21, 26.07, 22.38, 17.98, 17.24, 15.61, 14.96; ESI-HRMS (*m*/*z*) Calcd for $C_{75}H_{118}N_4O_{37}$ $[M + H]^+$: 1667.7475. Found 1667.7522.

*4.1.15. Synthesis of N-(2-((1-(6^A-deoxy-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)methoxy)ethyl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**24**)*

Prepared from **19** according to general procedure B, the residue was purified by RP flash chromatography (eluent: methanol) to afford **24** as a white foam with a yield of 80%. ^{1}H NMR (600 MHz, MeOD:$CDCl_3$ = 2:1): δ 8.03 (s, 1H), 5.63 (s, 1H), 5.10 (d, 1H, *J* = 3.6 Hz), 5.05 (dd, 1H, *J* = 14.2, 2.0 Hz), 4.99 (d, 1H, *J* = 3.7 Hz), 4.99–4.96 (m, 3H), 4.92 (dd, 1H, *J* = 7.6, 3.5 Hz), 4.65 (s, 2H), 4.58 (dd, 1H, *J* = 14.3, 8.5 Hz), 4.11–4.08 (m, 1H), 3.92–3.72 (m, 21H), 3.64 (t, 2H, *J* = 5.4 Hz), 3.57 (dd, 1H, *J* = 9.8, 3.5 Hz), 3.54–3.38 (m, 14H), 3.33–3.29 (m, 1H), 3.18 (dd, 1H, *J* = 11.8, 4.4 Hz), 3.03 (dd, 1H, *J* = 12.1, 3.1 Hz), 2.74 (td, 1H, *J* = 10.1, 3.3 Hz), 2.18–2.14 (m, 2H), 1.97–1.23 (m, other aliphatic ring protons), 1.43, 1.15, 1.14, 1.11 (s, each 3H, 4 × CH_3), 1.02 (dd, 1H, *J* = 13.9, 1.9 Hz), 1.00, 0.81, 0.78 (s, each 3H, 3 × CH_3), 0.77 (d, 1H, *J* = 11.7 Hz); ^{13}C NMR (150 MHz, MeOD:$CDCl_3$ = 2:1): δ 202.57, 178.93, 172.64, 145.66, 129.09, 127.21, 104.13, 104.00, 103.89, 103.87, 103.84, 103.79, 103.40, 85.18, 83.07, 82.97, 82.90, 82.84, 79.49, 79.40, 79.27, 79.05, 74.80, 74.72, 74.56, 74.42, 74.24, 74.21, 74.10, 73.91, 73.69, 73.64, 73.20, 72.13, 70.39, 64.74, 63.16, 61.85, 61.79, 61.11, 56.20, 52.46, 49.63, 46.71, 44.82, 44.59, 42.58, 40.42, 40.22, 40.19, 38.72, 38.33, 33.83, 32.89, 32.02, 29.55, 29.51, 29.23, 28.70, 27.84, 27.59, 27.44, 23.81, 19.36, 18.62, 17.01, 16.36; ESI-HRMS (*m*/*z*) Calcd for $C_{77}H_{122}N_4O_{38}$ $[M + H]^+$: 1711.7810. Found 1711.7784.

*4.1.16. Synthesis of N-(2-[2-((1-(6^A-deoxy-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)methoxy))ethoxy]ethyl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**25**)*

Prepared from **20** according to general procedure B, the residue was purified by RP flash chromatography (eluent: methanol) to afford **25** as a white foam with a yield of 82%. ^{1}H NMR (600 MHz, MeOD:$CDCl_3$ = 2:1): δ 8.13 (s, 1H), 5.67 (s, 1H), 5.12 (d, 1H, *J* = 3.6 Hz), 5.07 (dd, 1H, *J* = 14.9, 1.9 Hz), 4.99–4.96 (m, 4H), 4.93 (dd, 1H, *J* = 7.7, 3.5 Hz), 4.68 (s, 2H), 4.67 (dd, 1H, *J* = 14.6, 8.2 Hz), 4.12 (dt, 1H, *J* = 10.0, 2.2 Hz), 3.94–3.71 (m, 25H), 3.67 (t, 2H, *J* = 4.5 Hz), 3.54–3.38 (m, 17H), 3.37–3.29 (m, 3H), 3.16 (dd, 1H, *J* = 11.8, 4.4 Hz), 3.07 (dd, 1H, *J* = 12.2, 3.4 Hz), 2.73 (td, 1H, *J* = 10.2, 3.2 Hz), 2.46 (s, 1H), 2.19–2.14 (m, 2H), 1.97–1.02 (m, other aliphatic ring protons), 1.43 (s, 3H, CH_3), 1.14 (s, 6H, 2 × CH_3), 1.11, 1.00, 0.82, 0.80 (s, each 3H, 4 × CH_3), 0.77 (d, 1H, *J* = 11.4 Hz); ^{13}C NMR (150 MHz, MeOD:$CDCl_3$ = 2:1): δ 202.55, 178.88, 172.58, 145.26, 130.58, 130.39, 129.13, 127.60, 127.18, 120.46, 116.19, 104.06, 104.02,

103.87, 103.83, 103.78, 103.40, 85.05, 83.22, 83.07, 83.01, 82.90, 79.41, 74.82, 74.76, 74.73, 74.57, 74.42, 74.25, 74.22, 74.09, 73.98, 73.90, 73.69, 73.66, 73.29, 71.97, 71.21, 71.15, 70.79, 64.70, 63.16, 62.00, 61.90, 61.82, 61.24, 56.20, 52.80, 49.61, 49.57, 46.71, 44.83, 44.59, 42.61, 40.37, 40.31, 40.23, 38.77, 38.33, 33.83, 32.92, 32.02, 29.55, 29.51, 29.28, 28.70, 27.85, 27.60, 27.45, 23.79, 19.33, 18.63, 16.99, 16.35; ESI-HRMS (*m*/*z*) Calcd for $C_{79}H_{126}N_4O_{39}$ $[M + H]^+$: 1755.8077. Found 1755.8071.

4.1.17. Synthesis of N-(1-(1-(6^A-deoxy-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)-2,5,8,11-tetraoxatridecan-13-yl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**26**)

Prepared from **21** according to general procedure B, the residue was purified by RP flash chromatography (eluent: methanol) to afford **26** as a white foam with a yield of 98%. ^{1}H NMR (600 MHz, MeOD): δ 8.02 (s, 1H), 5.66 (s, 1H), 5.12 (d, 1H, *J* = 3.6 Hz), 4.99–4.96 (m, 4H), 4.93 (dd, 1H, *J* = 8.8, 3.4 Hz), 4.68–4.61 (m, 3H), 4.12 (t, 1H, *J* = 8.5 Hz), 3.93–3.62 (m, 37H), 3.58–3.44 (m, 18H), 3.37–3.33 (m, 2H), 3.18 (dd, 1H, *J* = 11.8, 4.5 Hz), 3.06 (dd, 1H, *J* = 12.4, 2.4 Hz), 2.72 (td, 1H, *J* = 10.1, 3.2 Hz), 2.45 (s, 1H), 2.21–1.02 (m, other aliphatic ring protons), 1.43 (s, 3H, CH_3), 1.14 (s, 6H, 2 × CH_3), 1.12, 1.00, 0.83, 0.81 (s, each 3H, 4 × CH_3), 0.76 (d, 1H, *J* = 11.3 Hz); ^{13}C NMR (150 MHz, MeOD): δ 202.39, 178.80, 172.42, 145.72, 130.84, 129.14, 127.19, 104.04, 103.89, 103.84, 103.38, 85.08, 83.21, 83.06, 83.00, 82.87, 82.77, 79.39, 74.80, 74.72, 74.70, 74.53, 74.45, 74.26, 74.23, 74.08, 73.91, 73.68, 73.64, 73.26, 72.07, 71.56, 71.52, 71.21, 70.97, 70.73, 65.01, 63.14, 61.92, 61.86, 61.83, 61.77, 56.19, 52.37, 49.48, 46.68, 44.82, 44.57, 42.61, 40.35, 40.22, 38.76, 38.32, 36.52, 33.83, 32.91, 32.03, 30.31, 29.51, 29.30, 28.71, 28.10, 27.83, 27.59, 27.45, 23.80, 19.34, 18.62, 16.98, 16.36; ESI-HRMS (*m*/*z*) Calcd for $C_{83}H_{134}N_4O_{41}$ $[M + H]^+$: 1843.8596. Found 1843.8595.

4.1.18. Synthesis of N-(1-(1-(6^A-deoxy-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)-2,5,8,11,14,17-hexaoxanonadecan-19-yl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**27**)

Prepared from **22** according to general procedure B, the residue was purified by RP flash chromatography (eluent: methanol) to afford **27** as a white foam with a yield of 90%. ^{1}H NMR (600 MHz, MeOD): δ 8.07 (s, 1H), 5.66 (s, 1H), 5.12 (d, 1H, *J* = 3.5 Hz), 5.05 (d, 1H, *J* = 13.6 Hz), 4.99–4.96 (m, 4H), 4.93 (dd, 1H, *J* = 6.7, 3.4 Hz), 4.70–4.64 (m, 3H), 4.12 (t, 1H, *J* = 8.9 Hz), 3.93–3.63 (m, 38H), 3.58–3.44 (m, 16H), 3.37–3.33 (m, 2H), 3.18 (dd, 1H, *J* = 11.8, 4.5 Hz), 3.07 (dd, 1H, *J* = 12.1, 2.9 Hz), 2.73 (td, 1H, *J* = 10.1, 3.2 Hz), 2.45 (s, 1H), 2.21–1.01 (m, other aliphatic ring protons), 1.43 (s, 3H, CH_3), 1.14 (s, 6H, 2 × CH_3), 1.12, 1.00, 0.83, 0.80 (s, each 3H, 4 × CH_3), 0.76 (d, 1H, *J* = 11.3 Hz); ^{13}C NMR (150 MHz, MeOD): δ 202.41, 178.81, 172.45, 145.55, 130.85, 129.15, 127.39, 104.03, 103.88, 103.83, 103.39, 85.05, 83.22, 83.06, 83.01, 82.89, 82.84, 79.41, 74.82, 74.76, 74.73, 74.56, 74.44, 74.26, 74.23, 74.09, 73.96, 73.90, 73.69, 73.66, 73.30, 72.01, 71.54, 71.22, 71.04, 70.73, 64.85, 63.15, 61.97, 61.86, 61.80, 61.18, 56.20, 52.58, 49.59, 46.69, 44.83, 44.58, 42.63, 40.36, 40.23, 38.77, 38.33, 36.47, 33.83, 33.05, 32.92, 32.03, 30.32, 29.50, 29.30, 28.71, 28.11, 27.84, 27.60, 27.46, 26.92, 23.80, 19.33, 18.63, 16.98, 16.36; ESI-HRMS (*m*/*z*) Calcd for $C_{87}H_{142}N_4O_{43}$ $[M + H]^+$: 1931.9121. Found 1931.9117.

4.1.19. N-(2-(piperazin-1-yl)-ethyl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**28**)

Prepared from **7** and 2-(piperazin-1-yl)ethan-1-amine according to general procedure C, the residue was purified by flash chromatography (eluent: DCM:MeOH:$NH_3 \cdot H_2O$ = 20:1:0.2) to afford **28** as a white solid with a yield of 45%. R_f = 0.35 (eluent: DCM:MeOH:$NH_3 \cdot H_2O$ = 20:1:0.2); m.p. 157–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (br s, 1H), 5.65 (s, 1H), 3.40–3.14 (m, 3H), 2.90 (t, 1H, *J* = 4.3 Hz), 2.71 (d, 1H, *J* = 13.1 Hz), 2.47–2.43 (m, 6H), 2.29 (s, 1H), 2.12 (t, 1H, *J* = 8.3 Hz), 2.00–1.00 (m, other aliphatic ring protons), 1.33 (s, 3H, CH_3), 1.07(s, 9H, 3 × CH_3), 0.95 (s, 3H, CH_3), 0.89 (d, 1H, *J* = 13.6 Hz), 0.76, 0,75 (s, each 3H, 2 × CH_3), 0.64 (d, 1H, *J* = 11.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.98, 175.75, 169.34, 128.35, 78.53, 61.85, 57.19, 54.97, 53.53, 48.11, 45.59, 45.37, 43.60, 43.20, 41.81, 39.28, 39.15, 37.49, 37.04, 35.60, 32.73, 31.86, 31.41, 29.62, 28.58, 28.15, 27.28, 26.43, 26.36, 23.42, 18.66, 17.46, 16.36, 15.67; ESI-HRMS (*m*/*z*) Calcd for $C_{36}H_{59}N_3O_3$ $[M + H]^+$: 582.4629. Found 582.4621.

4.1.20. Synthesis of N-(2-(4-(prop-2-yn-1-yl)piperzain-1-yl)ethyl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**29**)

To a solution of **28** (90 mg, 0.16 mmol) and bromopropyne (21.2 mg, 0.18 mmol) in dried THF, K_2CO_3 (40 mg, 0.29 mmol) was added. The resulting solution was vigorously stirred for 24 h at room temperature. The solvent was removed by steaming. The residue was purified by column chromatography to afford compound **29** as a yellow solid with a yield of 76%. R_f = 0.45 (DCM:MeOH:$NH_3 \cdot H_2O$ = 10:1:0.01); m.p. 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 (br s, 1H), 5.69 (s, 1H), 3.43–3.31 (m, 2H), 3.28 (d, 2H, *J* = 2.4 Hz), 3.21 (dd, 1H, *J* = 10.3, 5.2 Hz), 2.77 (td, 1H, *J* = 10.2, 3.2 Hz), 2.60–2.50 (m, 10H), 2.32 (s, 1H), 2.22 (t, 1H, *J* = 2.4 Hz), 2.18 (dd, 1H, *J* = 12.0, 5.8 Hz), 2.07–1.57 (m, 10H), 1.47–1.03 (m, other aliphatic ring protons), 1.37, 1.12 (s, each 3H, 2 × CH_3), 1.11(s, 6H, 2 × CH_3), 0.99 (s, 3H, CH_3), 0.93 (dd, 1H, *J* = 12.8, 4.4 Hz), 0.80, 0.79 (s, each 3H, 2 × CH_3), 0.68 (d, 1H, *J* = 11.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.83, 175.78, 169.10, 128.51, 78.87, 78.72, 73.04, 61.80, 56.46, 54.96, 52.67, 51.81, 48.00, 46.71, 45.35, 43.59, 43.17, 41.80, 39.17, 39.12, 37.51, 37.06, 35.81, 32.73, 31.87, 31.46, 29.63, 28.59, 28.09, 27.29, 26.42, 26.38, 23.41, 18.65, 17.45, 16.33, 15.57; ESI-HRMS (*m*/*z*) Calcd for $C_{39}H_{61}N_3O_3$ $[M + H]^+$: 620.4786. Found 620.4775.

4.1.21. Synthesis of N-(2-(4-((1-(6^A-deoxy-per-O-acetylated-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)-ethyl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**30**)

Prepared from **29** and **16** according to general procedure A, the residue was purified by flash chromatography (eluent: petroleum ether: acetone = 1:2) to afford **30** as a white foam with a yield of 42%. R_f = 0.10 (petroleum ether:acetone = 1:2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.56 (s, 1H), 6.27 (br s, 1H), 5.71 (s, 1H), 5.66 (d, 1H, *J* = 2.6 Hz), 5.37–5.16 (m, 10H), 5.12 (d, 1H, *J* = 4.0 Hz), 5.10 (d, 1H, *J* = 4.0 Hz), 5.07 (d, 1H, *J* = 3.6 Hz), 5.05 (d, 1H, *J* = 3.7 Hz), 5.01 (d, 1H, *J* = 3.5 Hz), 4.94 (dd, 1H, *J* = 8.6, 4.0 Hz), 4.85–4.81 (m, 3H), 4.75 (dd, 2H, *J* = 9.7, 3.6 Hz), 4.68 (dd, 1H, *J* = 12.1, 1.3 Hz), 4.60–4.45 (m, 7H), 4.32–4.06 (m, 13H), 3.78–3.62 (m, 8H), 3.58 (t, 1H, *J* = 9.1 Hz), 3.34 (d, 2H, *J* = 26.2 Hz), 3.21 (dd, 1H, *J* = 11.2, 4.9 Hz), 2.77 (td, 1H, *J* = 10.1, 3.7 Hz), 2.50 (s, 9H), 2.34 (s, 1H), 2.15–2.01 (m, 84H), 1.92–1.58 (m, 10H), 1.44–1.03 (m, other aliphatic ring protons), 1.38, 1.13, 1.12, 1.11, 1.00 (s, each 3H, 5 × CH_3), 0.96 (dd, 1H, *J* = 13.2, 3.7 Hz), 0.80, 0.79 (s, each 3H, 2 × CH_3), 0.69 (d, 1H, *J* = 11.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.9, 170.85, 170.75, 170.70, 170.63, 170.56, 170.51, 170.39, 170.27, 170.25, 169.60, 169.40, 169.37, 169.29, 169.27, 169.16, 144.25, 128.53, 125.73, 97.04, 96.78, 96.66, 96.53, 96.49, 96.38, 78.69, 77.03, 76.96, 76.80, 76.54, 76.49, 76.78, 71.61, 71.39, 71.34, 71.03, 70.94, 70.52, 70.41, 70.32, 70.13, 70.05, 69.99, 69.84, 69.67, 69.63, 69.53, 69.47, 69.25, 68.12, 62.78, 62.61, 62.58, 62.43, 62.21, 61.80, 56.37, 54.94, 52.64, 49.11, 47.95, 45.35, 43.59, 43.20, 41.83, 39.12, 39.10, 37.51, 37.07, 35.79, 32.75, 31.87, 31.52, 29.62, 28.59, 28.08, 27.30, 26.45, 26.42, 23.42, 20.84, 20.78, 20.74, 20.72, 20.70, 20.63, 20.60, 18.68; ESI-HRMS (*m*/*z*) Calcd for $C_{121}H_{170}N_6O_{57}$ $[M + H]^+$: 2620.0661. Found 2620.0632.

*4.1.22. Synthesis of N-(2-(4-((1-(6^A-deoxy-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)-ethyl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**31**)*

Prepared from **30** according to general procedure B, the residue was purified by RP flash chromatography (eluent: methanol) to afford **31** as a white foam with a yield of 90%. ^{1}H NMR (600 MHz, MeOD:$CDCl_3$ = 2:1): δ 7.97 (s, 1H), 5.67 (s, 1H), 5.08 (d, 1H, *J* = 3.1 Hz), 5.03 (d, 1H, *J* = 13.6 Hz), 4.96–4.94 (m, 4H), 4.91 (t, 2H, *J* = 4.3 Hz), 4.57 (dd, 3H, *J* = 13.7, 7.3 Hz), 4.13 (t, 1H, *J* = 8.6 Hz), 3.92–3.72 (m, 23H), 3.58–3.42 (m, 15H), 3.34–3.28 (m, 3H), 3.17 (dd, 1H, *J* = 11.8, 4.5 Hz), 2.79 (br s, 5H), 2.72 (td, 1H, *J* = 13.5, 3.6 Hz), 2.65 (t, 3H, *J* = 5.6 Hz), 2.43 (s, 1H), 2.17–2.10 (m, 2H), 1.99 (s, 1H), 1.94 (dd, 1H, *J* = 10.8, 2.5 Hz), 1.89–1.86 (m, 2H), 1.75–1.03 (m, other aliphatic ring protons), 1.42, 1.14, 1.13, 1.11, 0.99, 0.82, 0.79 (s, each 3H, 7 × CH_3), 0.74 (d, 1H, *J* = 11.7 Hz); ^{13}C NMR (150 MHz, MeOD:$CDCl_3$ = 2:1): δ 202.40, 178.76, 172.29, 128.95, 103.94, 103.87, 103.75, 103.68, 103.63, 103.28, 84.97, 82.90, 82.85, 82.70, 74.50, 74.44, 74.30, 74.13, 74.01, 73.97, 73.81, 73.62, 73.39, 73.34, 72.88, 71.83, 62.97, 61.60, 60.85, 57.75, 56.00, 53.01, 52.84, 46.54, 44.61, 44.38, 42.34, 40.21, 40.04, 38.54, 38.11, 36.89, 33.65, 32.73, 31.85, 29.55, 29.28, 28.59, 27.59, 27.38, 27.25, 23.84, 19.28, 18.39, 16.93, 16.23; ESI-HRMS (*m*/*z*) Calcd for $C_{81}H_{130}N_6O_{37}$ [M + H]$^+$: 1779.8554. Found 1779.8523.

*4.1.23. Synthesis of N-(4-ethynylphenyl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**32**)*

To a solution of **2** (669 mg, 1.42 mmol) and benzenamine (111 mg, 0.95 mmol) in DMF, DMAP (55 mg, 0.45 mmol) and EDC (362 mg, 1.90 mmol) were added. The resulting solution was vigorously stirred for 24 h at room temperature. The solvent was removed by steaming. The residue was purified by column chromatography to afford compound **32** as a white solid with a yield of 60%. R_f = 0.50 (petroleum ether:ethyl acetate = 1:1); m.p. 146–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.43 (m, 5H), 5.68 (s, 1H), 3.22 (dd, 1H, *J* = 10.3, 5.8 Hz), 3.03 (s, 1H), 2.79 (dt, 1H, *J* = 13.3, 3.0 Hz), 2.34 (s, 1H), 2.22 (dd, 1H, *J* = 13.8, 3.2 Hz), 2.10–1.59 (m, 11H), 1.50–0.85 (m, other aliphatic ring protons), 1.39, 1.24 (s, each 3H, 2 × CH_3), 1.12 (s, 6H, 2 × CH_3), 1.00, 0.82, 0.80 (s, each 3H, 3 × CH_3), 0.70 (d, 1H, *J* = 11.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.06, 174.08, 168.94, 138.39, 132.91, 128.61, 119.66, 117.72, 83.34, 78.75, 76.85, 61.85, 54.96, 48.14, 45.38, 44.66, 43.22, 41.73, 39.15, 39.12, 37.39, 37.08, 32.75, 31.99, 31.62, 29.28, 28.37, 28.09, 27.27, 26.41, 26.39, 23.40, 18.65, 17.45, 16.31, 15.54; ESI-HRMS (*m*/*z*) Calcd for $C_{38}H_{51}NO_3$ [M + H]$^+$: 570.3942. Found 570.3935.

*4.1.24. Synthesis of N-(4-(1-(6^A-deoxy-per-O-acetylated-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)phenyl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**33**)*

Prepared from **32** and **16** according to general procedure A, the residue was purified by flash chromatography (eluent: petroleum ether:acetone = 1:1) to afford **33** as a white foam with a yield of 59%. R_f = 0.20 (petroleum ether:acetone = 1:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.85 (d, 2H, *J* = 8.3 Hz), 7.60 (d, 2H, *J* = 8.5 Hz), 7.42 (br s, 1H), 5.69 (s, 1H), 5.62 (d, 1H, *J* = 3.7 Hz), 5.37–5.20 (m, 8H), 5.19 (d, 1H, *J* = 4.0 Hz), 5.14 (d, 1H, *J* = 4.0 Hz), 5.09 (d, 1H, *J* = 4.0 Hz), 5.08–5.06 (m, 2H), 5.01 (d, 1H, *J* = 3.6 Hz), 4.97 (dd, 1H, *J* = 8.8, 4.0 Hz), 4.84–4.81 (m, 3H), 4.77 (dd, 1H, *J* = 9.7, 3.7 Hz), 4.74 (dd, 1H, *J* = 9.8, 3.6 Hz), 4.71–4.69 (m, 2H), 4.61 (d, 1H, *J* = 11.5 Hz), 4.56–4.45 (m, 5H), 4.37–4.12 (m, 12H), 4.09 (dt, 1H, *J* = 9.4, 2.9 Hz), 3.79 (dd, 1H, *J* = 9.3, 7.3 Hz), 3.76–3.65 (m, 6H), 3.22 (dd, 1H, *J* = 11.0, 5.2 Hz), 2.83 (s, 1H), 2.79 (td, 1H, *J* = 13.6, 3.5 Hz), 2.28–2.25 (m, 1H), 2.15–1.97(m, 61H), 1.92–1.20 (m, other aliphatic ring protons), 1.39, 1.26 (s, each 3H, 2 × CH_3), 1.12 (s, 6H, 2 × CH_3), 1.06–1.04 (m, 1H), 1.00 (s, 3H, CH_3), 0.97 (dt, 1H, *J* = 12.7, 3.8 Hz), 0.83, 0.80 (s, each 3H, 2 × CH_3), 0.70 (d, 1H, *J* = 11.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.92, 173.94, 170.84, 170.72, 170.68, 170.63, 170.57, 170.54, 170.50, 170.41, 170.37, 170.34, 170.30, 169.61, 169.37, 169.35, 169.30, 169.19, 168.73, 146.93, 137.75, 128.66, 126.64, 126.36, 122.38, 120.26, 97.09, 97.05, 96.83, 96.68, 96.60, 96.48, 96.40, 78.74, 77.41, 77.29, 76.78, 76.71, 76.19, 75.82, 71.55, 71.52, 71.15, 70.98, 70.78, 70.43, 70.38, 70.33, 70.25, 70.18, 70.07, 69.98, 69.74, 69.64, 69.54, 69.53, 69.48, 69.44, 69.34, 62.75, 62.69, 62.57, 62.52, 62.33, 61.84, 54.94, 49.49, 48.03, 45.31, 44.56, 43.21, 41.80, 39.12, 37.46, 37.09, 32.76, 32.00, 31.70, 29.40, 28.40, 28.08, 27.29, 26.43, 23.40, 20.84, 20.83, 20.78, 20.74, 20.71, 20.66, 20.62, 18.67, 17.47, 16.32, 15.54; ESI-HRMS (*m*/*z*) Calcd for $C_{120}H_{160}N_4O_{57}$ [M + H]$^+$: 2569.9823. Found 2569.9827.

*4.1.25. Synthesis of N-(4-(1-(6^A-deoxy-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)phenyl)-3β-hydroxy-11-oxo-olean-12-en-30-amide (**34**)*

Prepared from **33** according to general procedure B, the residue was purified by RP flash chromatography (eluent: methanol) to afford **39** as a white foam with a yield of 86%. ^{1}H NMR (600 MHz, DMSO): δ 9.37 (s, 1H), 8.40 (s, 1H), 7.78 (d, 2H, *J* = 8.6 Hz), 7.71 (d, 2H, *J* = 8.8 Hz), 5.50 (s, 1H), 5.10 (d, 1H, *J* = 3.5 Hz), 4.93 (d, 1H, *J* = 12.8 Hz), 4.87–4.85 (m, 4H), 4.80 (dd, 1H, *J* = 9.0, 3.1 Hz), 4.61 (dd, 1H, *J* = 14.2, 8.2 Hz), 4.10 (d, 1H, *J* = 10.1 Hz), 3.76–3.52 (m, 22H), 3.42–3.30 (m, 13H), 3.25 (dd, 1H, *J* = 9.8, 3.0 Hz), 3.06–2.99 (m, 3H), 2.60 (td, 1H, *J* = 10.1, 3.2 Hz), 2.35 (s, 1H), 2.18–0.96 (m, other aliphatic ring protons), 1.40, 1.21 (s, each 3H, 2 × CH_3), 1.05 (2 × s, 6H, 2 × CH_3), 0.93, 0.77 (s, each 3H, 2 × CH_3), 0.72 (d, 1H, *J* = 10.6 Hz), 0.71 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO): δ 199.15, 174.63, 169.70, 146.18, 138.82, 127.50, 126.00, 125.44, 121.92, 120.78, 102.23, 102.10, 101.99, 101.89, 101.34, 83.53, 82.06, 81.55, 81.44, 80.86, 76.63, 73.21, 73.11, 73.06, 73.02, 72.95, 72.60, 72.48, 72.41, 72.34, 72.25, 72.18, 72.08, 71.87, 69.87, 61.24, 60.19, 60.03, 59.94, 59.85, 59.76, 58.66, 54.13, 50.57, 47.89, 44.88, 44.05, 42.97, 40.73, 38.81, 38.55, 37.33, 36.68, 32.18, 31.56, 30.42, 28.38, 28.17, 28.07, 26.98, 26.10, 25.92, 23.02, 18.38, 17.18, 16.21, 16.02; ESI-HRMS (*m*/*z*) Calcd for $C_{80}H_{120}N_4O_{37}$ [M + H]$^+$: 1729.7704. Found 1729.7715.

*4.1.26. Synthesis of N-(1-(6^A-deoxy-per-O-methylated-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)methyl-3β-hydroxy-11-oxo-olean-12-en-30-amide (**35**)*

Prepared from **8** and **17** according to general procedure A, the residue was purified by flash chromatography (eluent: petroleum ether:acetone = 1:1) to afford **35** as a white foam with a yield of 59%. R_f = 0.15 (petroleum ether:acetone = 1:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (s, 1H), 6.34 (br s, 1H), 5.66 (s, 1H), 5.33 (d, 1H, *J* = 3.2 Hz), 5.17 (d, 1H, *J* = 3.4 Hz), 5.16 (d, 1H, *J* = 3.5 Hz), 5.13–5.12 (m, 3H), 5.11 (d, 1H, *J* = 3.6 Hz), 4.94 (dd, 1H, *J* = 14.0, 3.7 Hz), 4.79 (d, 1H, *J* = 13.4 Hz), 4.50 (dq, 2H, *J* = 14.9, 4.9 Hz), 4.05–4.03 (m, 1H), 3.95–3.93 (m, 1H), 3.89–3.72 (m, 10H), 3.65–3.16 (m, 98H), 3.00 (dd, 2H, *J* = 9.8, 3.4 Hz), 2.78 (dt, 1H, *J* = 13.6, 3.5 Hz), 2.31 (s, 1H), 2.18–2.16 (m, 1H), 2.05–2.00 (m, 2H), 1.85–1.79 (m, 3H), 1.67–1.58 (m, 5H), 1.47–1.17 (m, other aliphatic ring protons), 1.36, 1.12, 1.11, 1.08 (s, each 3H, 4 × CH_3), 1.02–1.01 (m, 1H), 1.00 (s, 3H, CH_3), 0.96 (dt, 1H, *J* = 12.8, 4.0 Hz), 0.80, 0.79 (s, each 3H, 2 × CH_3), 0.69 (d, 1H, *J* = 11.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.90, 175.89, 168.84, 144.00, 128.57, 124.26, 99.17, 98.92, 98.85, 98.79, 98.76, 98.29, 82.34, 82.17, 82.02, 81.97, 81.90, 81.81, 81.77, 81.47, 81.08, 80.41, 80.25, 80.23, 79.82, 79.79, 79.03, 78.77, 71.60, 71.34, 71.31, 71.23, 71.05, 70.98, 70.96, 70.92, 70.82, 70.50, 70.23, 61.79, 61.73, 61.48, 61.45, 61.35, 61.32, 59.19, 59.09, 59.01, 58.97, 58.95, 58.68, 58.64, 58.59, 58.45, 58.36, 58.31, 54.95, 51.11, 47.92, 45.33, 43.52, 43.17, 41.60, 39.18, 39.12, 37.45, 37.07, 35.03, 32.77, 31.91, 31.87, 31.52, 29.34, 28.47, 28.09, 27.28, 26.45, 26.42, 23.35, 18.68, 17.48, 16.35, 15.55; ESI-HRMS (*m*/*z*) Calcd for $C_{95}H_{158}N_4O_{37}$ [M + H]$^+$: 1948.0678. Found 1948.0671.

*4.1.27. Synthesis of 3β-(prop-2-yn-1-yloxy)-11-oxo-olean-12-en-30-oic acid benzyl ester (**37**)*

A solution of **36** (342 mg, 0.61 mmol) in dry THF (20 mL) was cooled to 0 °C. Sodium hydride (96 mg, 2.4 mmol) was added, and the mixture was stirred for 1 h at 0 °C. Then, 3-bromopropyne was added, and the solution was stirred for 24 h at room temperature. The solvent of THF was evaporated, and the residue was purified by column chromatography to afford compound **37** as a white solid with a yield of 60%. $R_f = 0.65$ (petroleum ether:ethyl acetate = 4:1); m.p. 204–206 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.31 (m, 5H), 5.54 (s, 1H), 5.20 (d, 1H, *J* = 12.2 Hz), 5.09 (d, 1H, *J* = 12.2 Hz), 4.26–4.16 (m, 2H), 3.04 (dd, 1H, *J* = 4.3, 11.7 Hz), 2.81 (td, 1H, *J* = 3.1, 10.2 Hz), 2.36 (t, 1H, *J* = 2.3 Hz), 2.31 (s, 1H), 2.04–1.73 (m, 8H), 1.64–0.83 (m, other aliphatic ring protons), 1.34, 1.16, 1.13, 1.10, 1.01, 0.80, 0.73 (s, each 3H, 7 × CH_3), 0.70 (d, 1H, *J* = 10.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.24, 176.23, 169.07, 128.61, 128.50, 128.30, 128.25, 85.38, 80.92, 73.42, 66.22, 61.75, 56.21, 55.47, 48.18, 45.37, 43.97, 43.13, 41.02, 38.88, 38.77, 37.62, 36.98, 32.72, 31.75, 31.13, 28.39, 28.28, 28.06, 26.88, 26.36, 23.31, 18.65, 17.40, 16.36, 16.33; ESI-HRMS (*m*/*z*) Calcd for $C_{40}H_{54}O_4$ $[M + H]^+$: 599.4022. Found 599.4095.

*4.1.28. Synthesis of 3β-((1-(6^A-deoxy-per-O-acetylated-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)methoxy)-11-oxo-olean-12-en-30-oic acid benzyl ester (**38**)*

Prepared from **37** and **16** according to general procedure A, the residue was purified by flash chromatography (eluent: petroleum ether: acetone = 1:1) to afford **38** as a white foam with a yield of 60%. $R_f = 0.49$ (petroleum ether:acetone = 1:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.39–7.32 (m, 5H), 5.71 (d, 1H, *J* = 3.9 Hz), 5.52 (s, 1H), 5.38–5.26 (m, 7H), 5.20–5.18 (m, 3H), 5.13 (d, 1H, *J* = 4.1 Hz), 5.10–5.07 (m, 3H), 5.05 (d, 1H, *J* = 3.6 Hz), 5.01 (d, 1H, *J* = 3.6 Hz), 4.95 (dd, 1H, *J* = 3.9, 8.6 Hz), 4.85–4.81 (m, 3H), 4.78–4.74 (m, 3H), 4.67 (br d, 1H, *J* = 10.8 Hz), 4.61–4.50 (m, 7H), 4.46 (dd, 1H, *J* = 3.6, 10.5 Hz), 4.32–4.07 (m, 13H), 3.77–3.65 (m, 6H), 3.57 (t, 1H, *J* = 9.0 Hz), 3.00 (dd, 1H, *J* = 4.4, 11.7 Hz), 2.77 (td, 1H, *J* = 3.0, 13.5 Hz), 2.30 (s, 1H), 2.17–1.97 (m, 61H), 1.92 (dt, 1H, *J* = 3.6, 13.6 Hz), 1.84–1.72 (m, 8H), 1.63–1.53 (m, 5H), 1.33, 1.15, 1.12, 1.08, 0.90 (s, each 3H, 5 × CH_3), 1.43–0.86 (m, other aliphatic ring protons), 0.80, 0.72 (s, each 3H, 2 × CH_3), 0.68 (d, 1H, *J* = 11.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.17, 176.22, 170.85, 170.77, 170.74, 170.66, 170.59, 170.57, 170.53, 170.43, 170.39, 170.31, 170.28, 169.65, 169.45, 169.42, 169.33, 169.28, 168.95, 145.94, 136.10, 128.59, 128.47, 128.27, 128.22, 125.47, 97.23, 97.06, 96.78, 96.63, 96.53, 96.45, 96.40, 85.87, 77.04, 76.72, 76.63, 76.39, 75.78, 71.70, 71.35, 71.27, 71.03, 70.96, 70.53, 70.35, 70.13, 70.05, 69.82, 69.66, 69.64, 69.56, 69.48, 69.28, 66.20, 62.92, 62.82, 62.59, 62.54, 62.43, 62.24, 61.72, 55.23, 49.00, 48.19, 45.36, 43.97, 43.14, 41.02, 39.03, 38.88, 37.63, 36.98, 32.72, 31.75, 31.14, 28.38, 28.27, 28.04, 26.41, 26.37, 23.31, 22.74, 20.86, 20.85, 20.81, 20.80, 20.76, 20.74, 20.70, 20.65, 20.61, 18.65, 17.39, 16.44, 16.36; ESI-HRMS (*m*/*z*) Calcd for $C_{122}H_{163}N_3O_{58}$ $[M + H]^+$: 2598.9970. Found 2598.9980.

*4.1.29. Synthesis of 3β-((1-(6^A-deoxy-per-O-acetylated-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)methoxy)-11-oxo-olean-12-en-30-oic acid (**39**)*

A solution of compound **38** (50 mg, 0.019 mmol) in methanol was added catalytic amounts of Pd–C. The resulting solution was vigorously stirred for 24 h at 0.4 MPa under hydrogen environment. The solvent was removed by steaming. The residue was purified by column chromatography to afford compound **39** as a white foam with a yield of 76%. $R_f = 0.10$ (PE:Acetone = 1:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.60 (s, 1H), 5.71 (d, 1H, *J* = 3.9 Hz), 5.67 (s, 1H), 5.38–5.27 (m, 7H), 5.19–5.17 (m, 2H), 5.13 (d, 1H, *J* = 4.0 Hz), 5.09 (dd, 1H, *J* = 4.0, 9.8 Hz), 5.05 (d, 1H, *J* = 3.7 Hz), 5.01 (d, 1H, *J* = 3.6 Hz), 4.95 (dd, 1H, *J* = 4.0, 8.6 Hz), 4.86–4.74 (m, 7H), 4.67 (d, 1H, *J* = 11.0 Hz), 4.61–4.50 (m, 7H), 4.47 (dd, 1H, *J* = 3.6, 10.4 Hz), 4.32–4.24 (m, 7H), 4.20–4.08 (m, 8H), 3.78–3.66 (m, 7H), 3.58 (d, 1H, *J* = 9.1 Hz), 3.01 (dd, 1H, *J* = 4.2, 11.8 Hz), 2.78 (td, 1H, *J* = 3.3, 13.6 Hz), 2.33 (s, 1H), 2.19–2.01 (m, 68H), 1.93–1.90 (m, 1H), 1.84–1.73 (m, 3H), 1.36, 1.21, 1.13, 1.11, 0.91 (s, each 3H, 5 × CH_3), 1.64–1.00 (m, other aliphatic ring protons), 0.82, 0.80 (s, each 3H, 2 × CH_3), 0.70 (d, 1H, *J* = 11.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.40, 180.08, 170.86, 170.78, 170.75, 170.66, 170.60, 170.57, 170.53, 170.43, 170.39, 170.31, 170.28, 169.66, 169.45, 169.42, 169.33, 169.29, 129.90, 129.87, 128.47, 125.47, 97.23, 97.07, 96.80, 96.64, 96.55, 96.47, 96.41, 85.96, 77.41, 77.30, 76.78, 76.70, 76.40, 75.82, 71.71, 71.36, 71.28, 71.04, 70.96, 70.55, 70.37, 70.33, 70.16, 70.06, 69.83, 69.67, 69.65, 69.58, 69.53, 69.49, 69.30, 62.95, 62.84, 62.60, 62.55, 62.45, 62.26, 61.75, 55.27, 49.02, 48.27, 45.45, 43.75, 43.19, 41.03, 39.05, 38.89, 37.76, 37.02, 32.75, 31.85, 31.03, 29.75, 29.67, 29.59, 29.53, 29.50, 29.45, 29.35, 29.29, 29.21, 28.52, 28.44, 28.06, 26.46, 26.41, 23.37, 22.77, 20.87, 20.85, 20.79, 20.76, 20.74, 20.73, 20.70, 20.65, 20.61, 18.68, 17.40, 16.45; ESI-HRMS (*m*/*z*) Calcd for $C_{115}H_{157}N_3O_{58}$ $[M+H]^+$: 2508.9501. Found 2508.9487.

*4.1.30. Synthesis of 3β-((1-(6^A-deoxy-β-cyclodextrin-6-yl)-1H-1,2,3-triazol-4-yl)methoxy)-11-oxo-olean-12-en-30-oic acid (**40**)*

Prepared from **39** according to general procedure B, the residue was purified by RP flash chromatography (eluent: methanol) to afford **40** as a white foam with a yield of 81%. ^{1}H NMR (600 MHz, MeOD:$CDCl_3$ = 2:1): δ 7.93 (s, 1H), 5.61 (s, 1H), 5.09 (d, 1H, *J* = 3.7 Hz), 4.97–4.94 (m, 5H), 4.92 (d, 1H, *J* = 3.5 Hz), 4.90 (d, 1H, *J* = 3.6 Hz), 4.63 (dd, 1H, *J* = 14.5, 7.5 Hz), 4.13–4.10 (m, 1H), 3.92–3.71 (m, 20H), 3.56 (dd, 1H, *J* = 9.8, 3.5 Hz), 3.54–3.43 (m, 11H), 3.36 (dd, 1H, *J* = 10.8, 1.5 Hz), 3.11 (dd, 1H, *J* = 12.2, 3.1 Hz), 3.03 (dd, 1H, *J* = 11.7, 4.3 Hz), 2.77 (td, 1H, *J* = 10.0, 3.5 Hz), 2.43 (s, 1H), 2.20 (dd, 1H, *J* = 12.9, 3.6 Hz), 2.11 (dt, 1H, *J* = 13.6, 4.3 Hz), 1.96–1.22 (m, other aliphatic ring protons), 1.41, 1.17, 1.14, 1.13 (s, each 3H, 4 × CH_3), 1.04 (dd, 1H, *J* = 11.5, 2.3 Hz), 0.99 (dd, 1H, *J* = 13.8, 3.0 Hz), 0.97, 0.83, 0.81, (s, each 3H, 3 × CH_3), 0.76 (d, 1H, *J* = 11.5 Hz); ^{13}C NMR (150 MHz, MeOD:$CDCl_3$ = 2:1): δ 202.46, 180.23, 172.57, 146.19, 128.78, 126.85, 103.85, 103.82, 103.72, 103.66, 103.64, 103.20, 87.61, 84.62, 82.92, 82.79, 82.77, 82.74, 82.63, 82.54, 74.47, 74.40, 74.25, 74.18, 73.99, 73.95, 73.78, 73.59, 73.56, 73.34, 73.32, 73.29, 72.95, 71.69, 63.33, 62.87, 61.57, 61.50, 60.88, 56.34, 51.91, 49.85, 49.30, 49.09, 54, 44.65, 44.37, 42.14, 39.95, 39.86, 38.73, 38.05, 33.60, 32.75, 31.82, 29.11, 28.77, 28.64, 27.36, 27.19, 23.87, 23.54, 19.25, 18.28, 16.91; ESI-HRMS (*m*/*z*) Calcd for $C_{75}H_{117}N_3O_{38}$ $[M + H]^+$: 1668.7388. Found 1668.7393.

4.2. Cell culture and virus

H1N1 influenza virus A/WSN/33 (H1N1) was used in antiviral studies. It was propagated in MDCK cells in serum-free Eagle's minimum essential medium supplemented with 2 μg/μL trypsin and 1.2 mM bicarbonate. Titers of virus stocks were determined according to Reed and Muench (1938) in MDCK cells [41].

4.3. In vitro cytotoxicity assay

All of the reported conjugates were evaluated for cytotoxicity in MDCK cells. The cells (1×10^4 cells per well) were seeded into 96-well tissue culture plates and incubated at 37 °C for 24 h in an atmosphere of 5% CO_2 to allow the cells to adhere to the surface of the wells. Subsequently, the culture medium was replaced with fresh medium containing the compounds at the concentration of 50 μM in triplicate, and control wells contained the equivalent volume of the medium containing 1% DMSO. After 36 h of incubation at 37 °C in an atmosphere of 5% CO_2, CellTiter-Glo reagent was added, and the plates were read using a Tecan Infinite M2000 PRO™ plate reader.

4.4. CPE reduction assay

The assay was performed as described by Noah et al. [38] with some modifications. MDCK cells were seeded into 96-well plates, incubated overnight and infected with influenza virus (MOI = 0.1) suspended in DMEM supplemented with 1% FBS, test compound and 2 μg/mL TPCK-treated trypsin, with a final DMSO concentration of 1% in each well, followed by 40 h of incubation, CellTiter-Glo reagent was added, and the plates were read using a Tecan Infinite M2000 PRO™ plate reader.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmech.2019.01.074.

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