Bioorganic Chemistry 88 (2019) 102951

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Design and synthesis of the novel oleanolic acid-cinnamic acid ester derivatives and glycyrrhetinic acid-cinnamic acid ester derivatives with cytotoxic properties

Rui Wang[a,b,1], Wei Yang[a,1], Yiqing Fan[a], Wim Dehaen[b], Yang Li[c], Huijing Li[d], Wei Wang[a], Qingxuan Zheng[a], Qiyong Huai[a,*]

[a] Marine College, Shandong University, Weihai 264209, China
[b] Molecular Design and Synthesis, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, B-3001 Heverlee, Belgium
[c] Zhong Yuan Academy of Biological Medicine, Liaocheng People's Hospital/Affiliated Liaocheng Hospital, Taishan Medical University, Liaocheng, China
[d] School of Marine Science and Technology, Harbin Institute of Technology at Weihai, Weihai 264209, China

ARTICLE INFO

Keywords:
Cytotoxicity
Oleanolic acid-cinnamic acid ester derivatives
Glycyrrhetinic acid-cinnamic acid ester derivatives
Apoptosis
ROS
Autophagy

ABSTRACT

Oleanolic acid (OA) and glycyrrhetinic acid (GA) are natural products with anticancer effects. Cinnamic acid (CA) and its derivatives also exhibited certain anticancer activity. In order to improve the anticancer activity of OA and GA, we designed and synthesized a series of novel OA-CA ester derivatives and GA-CA ester derivatives by using molecular hybridization approach. The 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay was used to assess their *in vitro* cytotoxicity on three cell lines (HeLa (cervical cancer), MCF-7 (breast cancer) and L-O2 (a normal hepatic cell)). Among the evaluated compounds, **3o** presented the strongest selective cytotoxicity on HeLa cells (IC_{50} = 1.35 μM) and showed no inhibitory activity against MCF-7 cells (IC_{50} > 100 μM) and L-O2 cells (IC_{50} > 100 μM), and **3e** presented the strongest selective inhibition of the MCF-7 cells (IC_{50} = 1.79 μM). What's more, compound **2d** also showed very strong selective inhibitory activity against HeLa cells (IC_{50} = 1.55 μM). The further research using Hoechst 33342, AO/EB dual-staining, flow cytometric analysis and DCFH-DA fluorescent dye staining assay presented that **2d** and **3o** could induce HeLa cells apoptosis and autophagy.

1. Introduction

Cancer has become a major cause of death in humans. In 2018, there were an estimated 18.1 million new cancer cases and 9.6 million cancer deaths worldwide [1]. In the United States, 1,735,350 new cancer cases and 609,640 cancer deaths are projected to occur in 2018 [2]. Efforts to develop low-toxic and high-efficiency anticancer agents have become the primary task of mankind. Natural products have long been used to treat various diseases due to their wide range of pharmacological activities [3]. Because of the structurally modified derivatives of natural products with anticancer effects have fewer side effects, they are being beneficial to combat cancer compare with synthetic drugs [4]. And it is a simple and effective method to obtain anticancer agents by structurally modifying natural products with antitumor activity [5]. Oleanolic acid (OA) and glycyrrhetinic acid (GA) are active natural products extracted from natural plants *Ligustri Lucidi Fructus* and *Glycyrrhiza uralensis*, respectively. They are all pentacyclic triterpenoids with similar structures (Fig. 1). Studies reported that they both have a wide range of pharmacological activities, such as antiviral [6–9], anticancer [10–15], anti-inflammatory [16–21] and some other activities [22–25]. The researchers did a lot of OA and GA structural modification work and achieved good results [26–34]. Jin et al. designed and prepared a series of glycyrrhetinic acid conjugates with a triphenylphosphonium cation (TTP^+) moiety and the novel glycyrrhetinic acid derivatives exhibited stronger anticancer cell proliferation than GA [35]. Chu et al. reported that oleanolic acid-lysine derivative derivatives displayed strong inhibitory effect on hepatic stellate cells and could induce it apoptosis [36]. Cinnamic acid (CA), as a natural product, was found to have certain inhibitory activity against cancer cells (such as lung cancer, prostate, melanoma and glioblastoma cells) [37–39].

In order to further enhance cytotoxic potency and better cancer cell/normal cell selectivity of OA and GA, a series of novel OA-CA ester

* Corresponding author.
E-mail addresses: lihuijing@iccas.ac.cn (H. Li), huaiqy01@163.com (Q. Huai).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.bioorg.2019.102951
Received 2 February 2019; Received in revised form 23 April 2019; Accepted 23 April 2019
Available online 27 April 2019

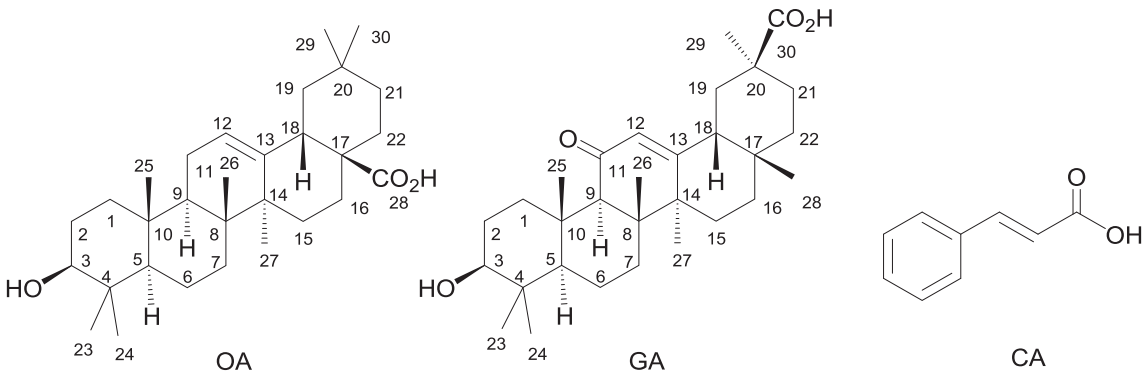


Fig. 1. Oleanolic acid (OA), glycyrrhetinic acid (GA) and cinnamic acid (CA).

derivatives and GA-CA ester derivatives modified on -OH and -COOH position were synthesized and used MTT method to test their inhibitory activities against HeLa, MCF-7 and L-O2 cells. To further study the mechanism of action of compounds **2d** and **3o** that we performed apoptosis, ROS accumulation and autophagy tests.

2. Results and discussion

2.1. Chemistry

The preparation of oleanolic acid-cinnamic acid ester derivatives **3a-p** was showed in Scheme 1. 2-substituted benzyl bromide or 2-substituted benzyl chloride respectively reacts with OA to obtain OA esters **2a-d**. Cinnamic acid, 4-position cinnamic acid with substituent and 5-fluorocinnamic acid were coupled with the 3-OH position of **2a-d** to obtain esters **3a-p** in 1-ethyl-(3-(3-dimethiylamino) propyl)-carbodiimide hydrochloride (EDCI)/ *N*, *N*-dimethyl-4-aminopyridine (DMAP) system. Showed in Scheme 2, glycyrrhetinic acid-cinnamic acid ester derivatives, viz., **5a-q** were prepared. The GA esters **4a-d** was obtained by the same way as OA esters **2a-d**. The 3-OH position of **4a-d** was coupled with cinnamic acid, 5-fluorocinnamic acid and 4-position cinnamic acid with substituent in the presence of EDCI/DMAP to get GA esters **5a-q**.

2.2. In vitro cytotoxicity

The *in vitro* cytotoxicity of compounds **1a, b**, **2a-d**, **3a-p**, **4a-d** and **5a-q** against L-O2, MCF-7 and HeLa cells were tested in MTT method and the result set out in Table 1. The lead compounds GA and OA displayed very poor inhibitory effect on MCF-7 and HeLa cells. In contrast to GA and OA, the OA esters **2a-d** and GA esters **4a-d** showed certain cytotoxicity to HeLa and MCF-7 cells, advocating that the introduction of a benzyl group with a substituent at the ortho position on the phenyl ring at COOH position of GA and OA could enhance their anticancer activity. In particular, compound **2d** showed strong selective inhibitory activity against HeLa cells (IC_{50} = 1.55 μM). Further modifying the OH group of OA esters or GA esters to obtain OA-CA esters derivatives or GA-CA esters derivatives, and their selective inhibitory activity against cancer cells was significantly improved. As compared with GA and OA, compound **3e**, **3m**, **5e**, **5i-j** and **5m** indicated strong selective inhibition of MCF-7 cells and compound **3e** was the best one with IC_{50} values 1.79 μM, advocating that 4-methylcinnamic acid linked to C-OH position of OA-2-chlorobenzyl ester could significantly improve the inhibition property of OA on MCF-7 cells. In HeLa cells, compounds **3k-l**, **3n-o**, **5d**, **5l** and **5o-q** exhibited strong selective inhibitory activity against it and compound **3o** was the most potent one with IC_{50} value 1.35 μM. Compound **3o** exhibited cytotoxicity close to the positive control Gefitinib (IC_{50} = 1.28 μM), however, its cytotoxicity against L-O2 cells (IC_{50} > 100 μM) was much less than that of Gefitinib (IC_{50} = 7.58 μM). Compounds **3m** and **5a** showed moderate inhibitory effect on HeLa and MCF-7 cells. Interestingly, compounds **3a**, **3c-d**, **3g-j**, **5c** and **5f** could inhibit neither HeLa cells nor MCF-7 cells.

Structure activity relationship analysis demonstrated that, there was no clear trend for the electron-donating and electron-withdrawing substituents for the effect of benzyl on GA cytotoxicity. However, the introduction of a benzyl group with an electron donating group (CH_3) in the ortho position to OA can significantly increase the inhibitory effect of OA on HeLa cells.

2.3. Inhibition of compound *2d* and *3o* on HeLa cells proliferation

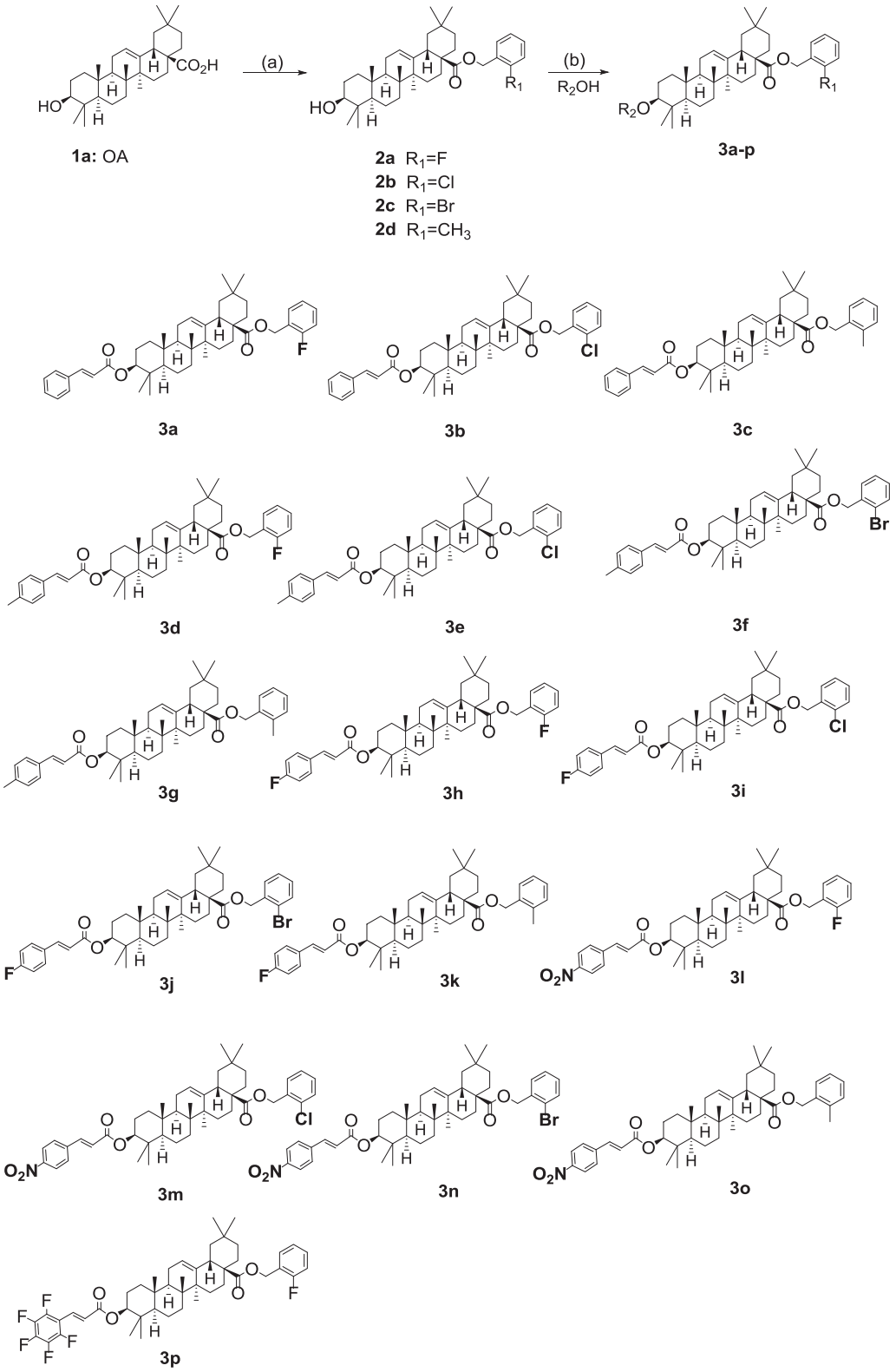
Since compounds **2d** and **3o** showed strong cytotoxicity against HeLa cells, we used HeLa cells to further study the mechanism of action of **2d** and **3o**. As shown in Fig. 2, compounds **2d** and **3o** have a significant inhibitory effect on the growth of HeLa cells and inhibit cell proliferation in a concentration- and time-dependent manner.

2.4. Cell apoptosis induced by compounds *2d* and *3o*

Apoptosis and necrosis, especially the former, are common cellular responses to anticancer drugs. To further evaluate whether the cytotoxic effect of **2d** and **3o** are related to apoptosis, we detected cell apoptosis by Hoechst 33342, AO/EB dual-staining and detected apoptosis rate by Annexin V/7-AAD dual-staining method (Figs. 3–5). After treatment with compounds **2d** (0 μM for control, 2 and 4 μM) and **3o** (0 μM for control, 1 and 2 μM) for 48 h, as shown in Fig. 3, a large number of cells with apoptotic features such as nuclear fragmentation and chromatin condensation were observed in the test group in a dose-dependent manner compared with the control group. AO, as a vital dye showing green fluorescence, can stain both live and dead cells. EB stains only apoptotic or necrotic cells that have lost their membrane integrity and appear red fluorescence. As shown in Fig. 4, in control cells the normal morphology and homogeneous green fluorescence were obtained. When cells were pre-incubated with compounds **2d** and **3o**, the orange or red fluorescence, which are the clearly morphological features of apoptosis, were observed in the test group in a dose-dependent manner. These preliminary results indicate that both compounds **2d** and **3o** can induce apoptosis of HeLa cells. To further confirm the nature of cell death induced by compounds **2d** and **3o**, Annexin V-PE/7-AAD dual-staining was performed, and the results were analyzed using flow cytometry. Fig. 5 shows that the population of apoptotic cells treated with compounds **2d** and **3o** had increased remarkably with dose-dependent relation.

2.5. Intracellular ROS accumulation induced by compounds *2d* and *3o*

ROS, which regard as mediators of apoptosis, are important for the induction of apoptosis in many cancer cells, and could enter the nucleus to cause DNA damage. Fluorescence microscopy was performed using DCFH-DA fluorescent dye to investigate whether compounds **2d** and **3o**

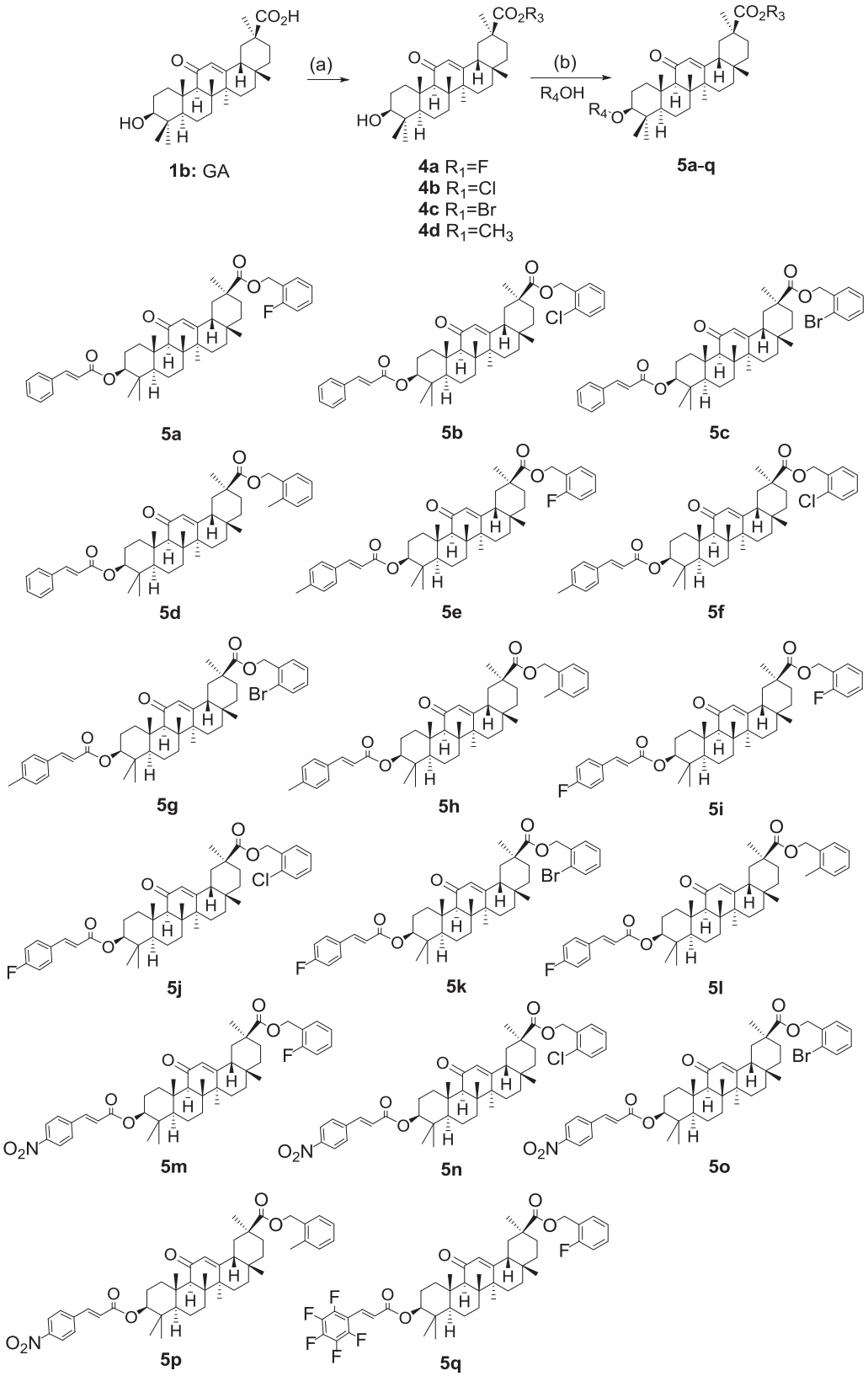


Scheme 1. General experimental way for the synthesis of **3a-p**. Reagents and conditions: (a) DMF, K_2CO_3, room temp; (b) EDCI, DMAP, reflux, room temp.

treatment could increase the ROS level in HeLa cells. As shown in Fig. 6, no significant fluorescence was found in control group. After treatment with compounds **2d** (2 and 4 μM) or **3o** (1 and 2 μM) for 48 h, the fluorescence images are observed. These results demonstrate that compounds **2d** and **3o** can increase ROS levels and in a dose-dependent manner.

2.6. Autophagy induced by compounds *2d* and *3o*

Autophagy, as a lysosomal degradation pathway, which is considered to be a third mode of cell death besides apoptosis and necrosis, is essential for homeostasis under normal conditions. To investigate the autophagic effect of those derivatives on HeLa cells, the cells were



Scheme 2. General experimental way for the synthesis of **5a-q**. Reagents and conditions: (a) DMF, K_2CO_3, room temp; (b) EDCI, DMAP, reflux, room temp.

treated with compounds **2d** (0 μM for control, 2 and 4 μM) and **3o** (0 μM for control, 1 and 2 μM) for 48 h, then the cells were stained with monodansylcadaverine (MDC). As shown in Fig. 7, different concentrations of compounds **2d** lead to an increase in MDC fluorescent intensity, with MFI = 1405 for 0 μM as the control, MFI = 2615 for 2 μM and MFI = 3446 for 4 μM. The same effect was also observed in compounds **3o** with MFI = 1338 for 0 μM as the control, MFI = 2222 for 1 μM and MFI = 2714 for 2 μM. The increase of MDC fluorescent

Table 1
The IC_{50} values of OA, GA and their derivatives toward L-O2, MCF-7 and HeLa cells.

Compd.	IC_{50} (μM)[a]			Compd.	IC_{50} (μM)[a]		
	L-O2	MCF-7	HeLa		L-O2	MCF-7	HeLa
1a	32.9	> 100	> 100	**4a**	69.43	27.73	42.68
1b	> 100	64.16	98.99	**4b**	11.9	14.06	19.01
2a	> 100	12.97	> 100	**4c**	1.9	20.07	22.01
2b	> 100	> 100	> 100	**4d**	44.2	8.21	29.99
2c	> 100	38.03	> 100	**5a**	23.57	18.61	37.46
2d	> 100	32.49	1.55	**5b**	7.38	> 100	42.97
3a	> 100	> 100	> 100	**5c**	10.19	> 100	> 100
3b	2.78	> 100	61.86	**5d**	83.18	> 100	1.69
3c	> 100	> 100	> 100	**5e**	> 100	36.84	> 100
3d	> 100	> 100	> 100	**5f**	> 100	> 100	> 100
3e	> 100	1.79	> 100	**5g**	28.19	> 100	61.35
3f	16.86	48.01	> 100	**5h**	25.31	> 100	> 100
3g	> 100	> 100	> 100	**5i**	> 100	46.53	> 100
3h	> 100	> 100	> 100	**5j**	> 100	86.55	> 100
3i	83.35	> 100	> 100	**5k**	69.6	19.36	> 100
3j	> 100	> 100	> 100	**5l**	> 100	81.96	1.72
3k	> 100	> 100	2.18	**5m**	> 100	42.68	> 100
3l	> 100	> 100	44.28	**5n**	1.77	> 100	40.45
3m	> 100	38.89	56.29	**5o**	> 100	> 100	2.76
3n	> 100	> 100	2.34	**5p**	> 100	> 100	53.42
3o	> 100	> 100	1.35	**5q**	64.31	> 100	55.81
3p	82.81	> 100	41.87	**Gefitinib**	7.58	1.22	1.28

[a] IC_{50} is the drug concentration effective in inhibiting 50% of the cell growth tested in MTT way and it was from three independent experiments.

intensity demonstrates the increasing number of autophagic cells. The results indicated that the derivatives could induce autophagy in HeLa cells and the autophagic effect occurs in a concentration-dependent manner.

3. Conclusion

In this study, a series of new OA-CA ester derivatives and GA-CA ester derivatives were prepared by using the molecular hybridization approach and were screened for their *in vitro* cytotoxic activity in the MTT method with MCF-7, HeLa and L-O2 cells. Compounds **2d** and **3o** displayed strong selective inhibitory effect on Hela cells with IC_{50} values 1.55 μM and 1.35 μM, respectively. A series of pharmacological studies showed that ROS was involved in the cytotoxicity and apoptosis induced **2d** and **3o**, and they also could induce Hela cells autophagy. Compound **3o** may be a potential new anti-Hela candidate drug. For MCF-7 cell, compound **3e** was the most potent one. Due to its strong selective inhibitory activity and it may be a potential anti-MCF-7 candidate agent. These derivatives will widen the structural diversity of anticancer targets and affirm the perspectives of further investigations.

4. Experimental

4.1. General

Melting points (mp) were tested by SGW X-4 micro-melting point apparatus. Silica gel and silica gel plates were used to perform Column chromatography and Thin-layer chromatography (TLC) respectively. Bruker-400 instrument (400 MHz) was used to get ^{13}C- and ^{1}H NMR spectra and $CDCl_3$ as solvent. Mass spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). The solvent and reagents without further purification and were obtained from Xinyue Chemical and Glass Co. (Weihai, China).

4.2. Synthesis

4.2.1. General experimental way for the synthesis of 2a-d and 4a-d

To a stirred solution of anhydrous potassium carbonate (500 mg, 3.62 mmol) and **1a (**or **1b)** (1 mmol) in *N*, *N*-dimethylformamide (DMF) (10 mL) at 25 °C for 0.5 h. 2-fluorobenzyl bromide (or 2-chlorobenzyl chloride, 2-bromobenzyl bromide and 2-methylbenzyl chloride) (1.5 mmol) was added and stirring was continued at 25 °C for 8 h. Saturated sodium chloride (10 mL) was added after the reaction was completed, and then extracted with ethyl acetate (50 mL) three times. The organic phase was washed with water. And the solvent was removed after drying over anhydrous sodium sulfate to get compounds **2a-d** or **4a-d**.

4.2.1.1. 2-Fluorobenzyl 3beta-hydroxyolean-12-en-28-oate ***(2a)***. White solid, yield 88%, mp 179.1–180.5 °C. ^{1}H NMR ($CDCl_3$) *δ*: 7.23– 7.43 (m, 2H), 6.99–7.19 (m, 2H), 5.28 (s, 2H, Ph-$\mathbf{H}_2$), 5.14 (m, 1H, H-12), 3.19 (dd, 1H, H-3, *J* = 10.6, 5.0 Hz), 2.89 (dd, 1H, H-18, *J* = 13.9, 4.5 Hz), 2.03 (m, 1H, H-16), 1.83 (dd, 2H, H-11 and H-11′, *J* = 8.9, 3.7 Hz), 1.74 (m, 1H, H-22), 1.69 (dd, 1H, H-1, *J* = 13.6, 4.4 Hz), 1.64 (m, 1H, H-19), 1.63 (m, 1H, H-16′), 1.60 (m, 1H, H-15), 1.55–1.58 (m, 2H, H-2 and H-2′), 1.53 (m, 1H, H-22′), 1.52 (m, 1H, H-6), 1.50 (m, 1H, H-9), 1.48 (m, 1H, H-6′), 1.42 (m, 1H, H-7), 1.39 (m, 1H, H-21), 1.34 (m, 1H, H-21′), 1.24 (m, 1H, H-7′), 1.17 (m, 1H, H-19′), 1.12 (s, 3H, H-27), 1.05 (m, 1H, H-1′), 1.02 (m, 1H, H-15′), 0.98 (s, 3H, H-30), 0.92 (s, 3H, H-29), 0.90 (m, 3H, H-23), 0.87 (s, 3H, H-25), 0.77 (s, 3H, H-24), 0.70 (m, 1H, H-5), 0.58 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) *δ*: 177.3, 159.8, 143.5, 130.6, 129.9, 129.9, 124.0, 122.5, 115.4, 78.9, 60.0, 55.2, 47.6, 46.8, 45.8, 41.7, 41.4, 39.3, 38.7, 38.5, 37.0, 33.9, 33.1, 32.7, 32.3, 30.7, 28.1, 27.3, 25.9, 23.6, 23.4, 23.0, 18.3, 16.8, 15.7. HRMS (ES +) *m/z* calcd for $C_{37}H_{54}F_1O_3$ $[M + H]^+$: 565.4051, found 581.4060.

4.2.1.2. 2-Chlorobenzyl 3beta-hydroxyolean-12-en-28-oate ***(2b)***. White solid, yield 86%, mp 184.1–185.2 °C. ^{1}H NMR ($CDCl_3$) *δ*: 7.36– 7.45

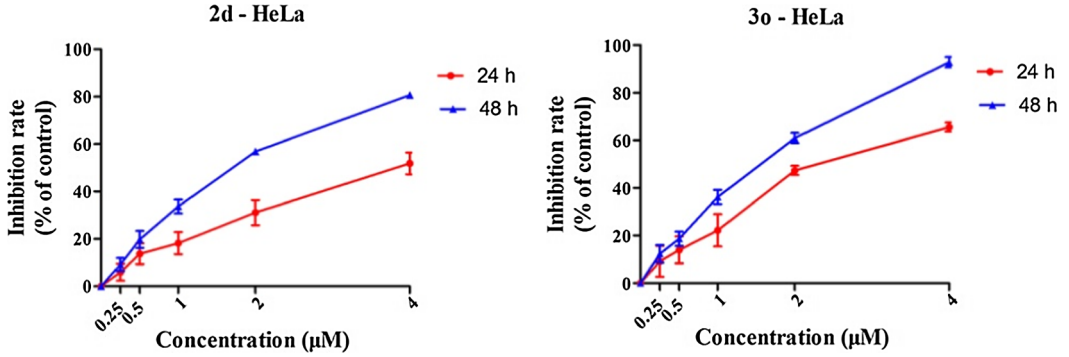


Fig. 2. The proliferation inhibition of **2d** and **3o** toward HeLa assayed by MTT. HeLa cells were continuously treated with different concentrations (0 μM, 0.25 μM, 0.5 μM, 1 μM, 2 μM, 4 μM) of **2d** and **3o** for 24 h or 48 h. Cell viability was then determined by MTT assay. The experiments were done three times and the results of representative experiments were displayed.

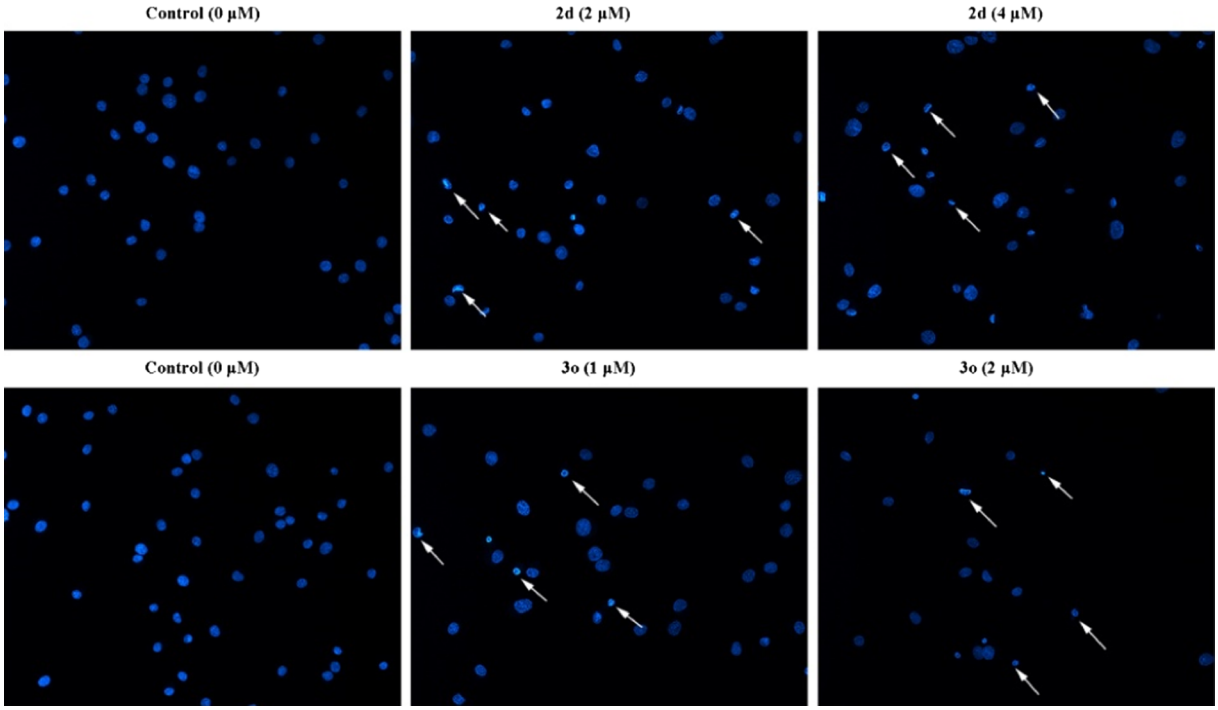


Fig. 3. Fluorescent microscopic analysis of nuclei fragmentation of Hoechst 33,342 staining. Representative photomicrographs of HeLa cells stained with Hoechst 33,342 fluorescent dye after exposure to **2d** (drug concentrations were 0 μM, 2 μM and 4 μM) and **3o** (0 μM, 1 μM and 2 μM) for 48 h. The experiments were done three times and the results of representative experiments were displayed.

(m, 2H), 7.24–7.26 (m, 2H), 5.29 (s, 2H, Ph-$\mathbf{H}_2$), 5.15 (m, 1H, H-12), 3.20 (dd, 1H, H-3, J = 10.6, 5.0 Hz), 2.91 (dd, 1H, H-18, J = 14.0, 8.0 Hz), 2.02 (m, 1H, H-16), 1.82–1.85 (m, 2H, H-11 and H-11′), 1.71 (m, 1H, H-22), 1.68 (m, 1H, H-1), 1.65 (m, 1H, H-19), 1.61 (m, 1H, H-16′), 1.59 (m, 1H, H-15), 1.56–1.58 (m, 2H, H-2 and H-2′), 1.55 (m, 1H, H-22′), 1.53 (m, 1H, H-6), 1.51 (m, 1H, H-9), 1.48 (m, 1H, H-6′), 1.43 (m, 1H, H-7), 1.39 (m, 1H, H-21), 1.34 (m, 1H, H-21′), 1.25 (m, 1H, H-7′), 1.18 (m, 1H, H-19′), 1.13 (s, 3H, H-27), 1.07 (m, 1H, H-1′), 1.03 (m, 1H, H-15′), 0.98 (s, 3H, H-30), 0.93 (s, 3H, H-29), 0.90 (s, 3H, H-23), 0.87 (s, 3H, H-25), 0.77 (s, 3H, H-24), 0.72 (m, 1H, H-5), 0.58 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) δ: 177.3, 143.6, 134.0, 133.8, 130.1, 129.4, 129.3, 126.7, 122.6, 78.9, 63.5, 55.2, 47.6, 46.9, 45.9, 41.7, 41.4, 39.3, 38.7, 37.0, 33.9, 33.1, 32.7, 32.4, 30.7, 28.1, 27.2, 25.9, 23.7, 23.4, 23.1, 18.3, 16.9, 15.6. HRMS (ES +) m/z calcd for $C_{37}H_{54}Cl_1O_3$

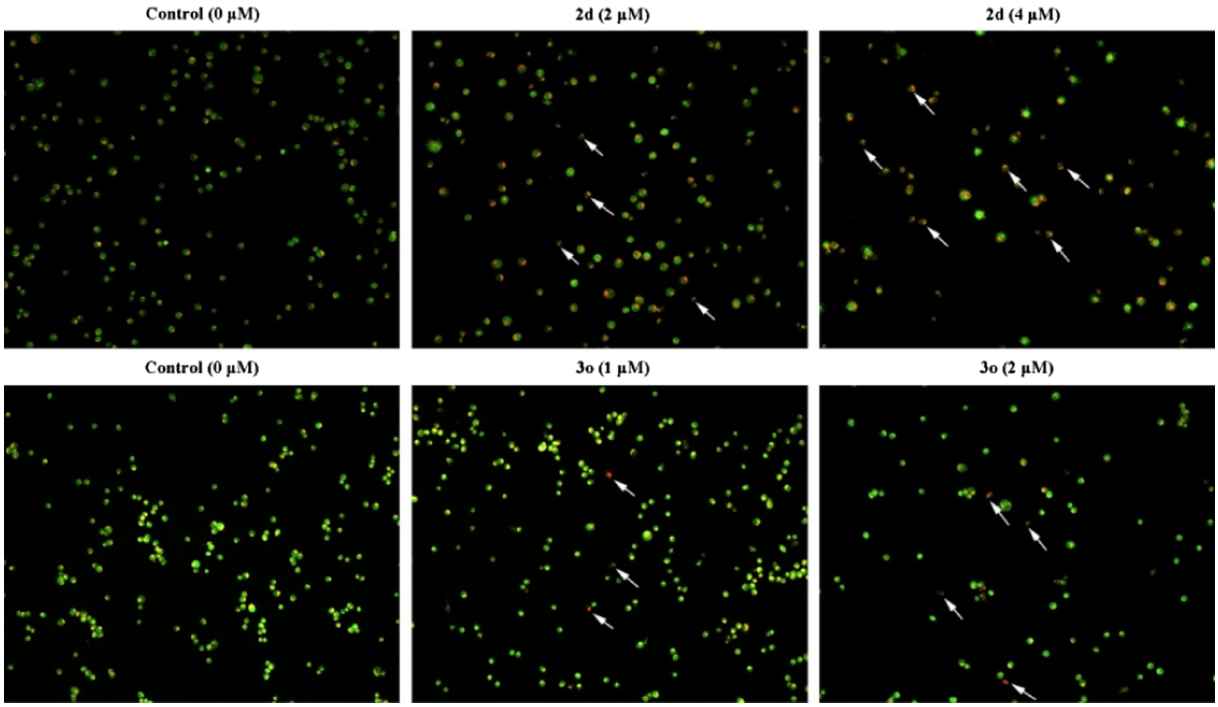


Fig. 4. Representative images of AO/EB double stained HeLa cells after treatment with compounds **2d** (drug concentrations were 0 μM, 2 μM and 4 μM) and **3o** (0 μM, 1 μM and 2 μM) for 48 h. The experiments were done three times and the results of representative experiments were displayed.

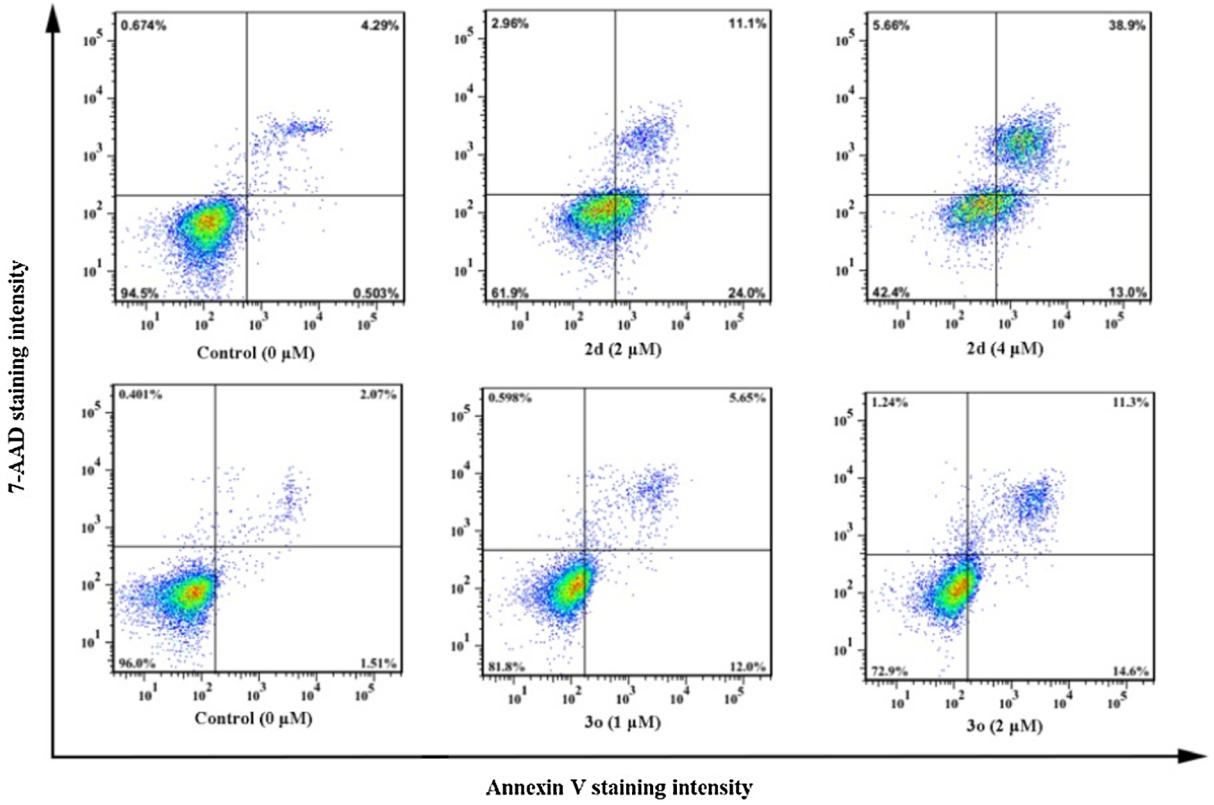


Fig. 5. HeLa cells apoptosis was detected by Annexin V/7-AAD assay after co-incubation with various concentrataions of **2d** (drug concentrations were 0 μM, 2 μM and 4 μM) and **3o** (0 μM, 1 μM and 2 μM) for 48 h. The experiments were done three times and the results of representative experiments were displayed.

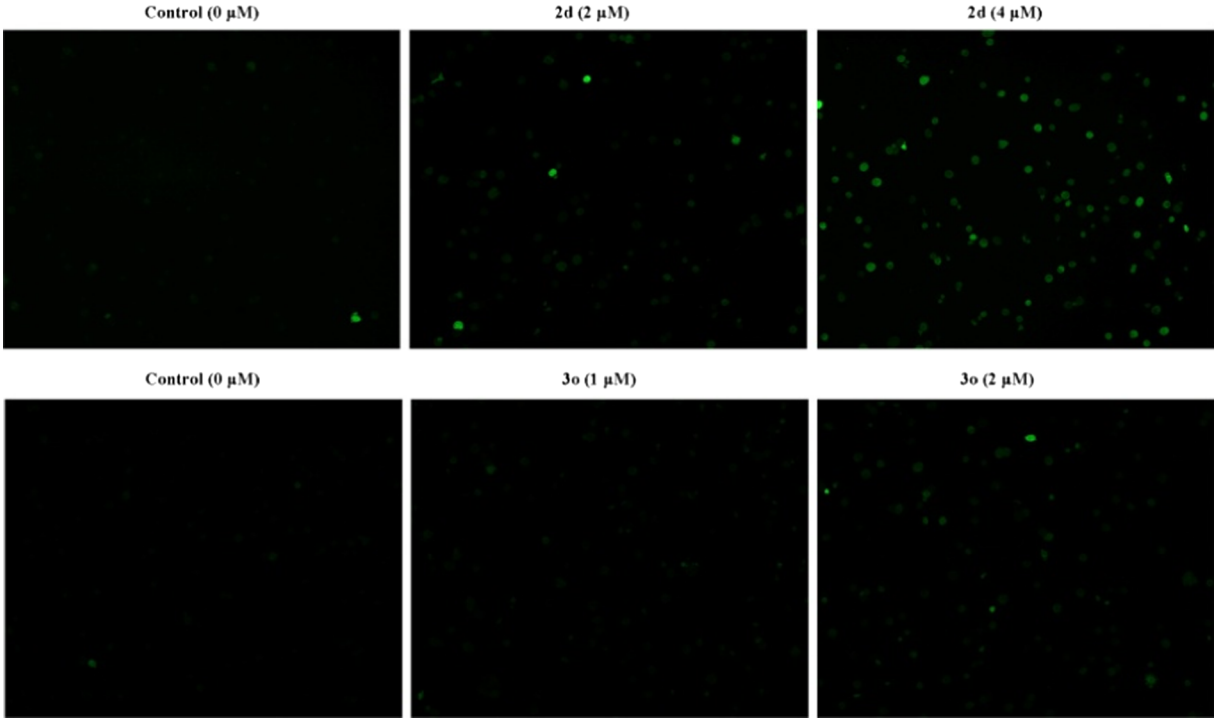


Fig. 6. Fluorescence microscope analysis of ROS by DCFH-DA staining after treatment with compounds **2d** (drug concentrations were 0 μM, 2 μM and 4 μM) and **3o** (0 μM, 1 μM and 2 μM) for 48 h. The experiments were done three times and the results of representative experiments were displayed.

$[M + H]^+$: 581.3756, found 581.3729.

*4.2.1.3. 2-Bromobenzyl 3beta-hydroxyolean-12-en-28-oate (**2c**)*. White solid, yield 85%, mp 169.1–170.4 °C. ^{1}H NMR ($CDCl_3$) δ: 7.34– 7.36 (m, 1H), 7.14–7.32 (m, 3H), 5.29 (s, 2H, Ph-$\mathbf{H}_2$), 5.10 (m, 1H, H-12), 3.21 (dd, 1H, H-3, J = 10.6, 5.0 Hz), 2.92 (dd, 1H, H-18, J = 13.9, 4.5 Hz), 2.00 (m, 1H, H-16), 1.85 (dd, 2H, H-11 and H-11′, J = 8.9, 3.7 Hz), 1.72 (m, 1H, H-22), 1.70 (dd, 1H, H-1, J = 13.6, 4.4 Hz), 1.66

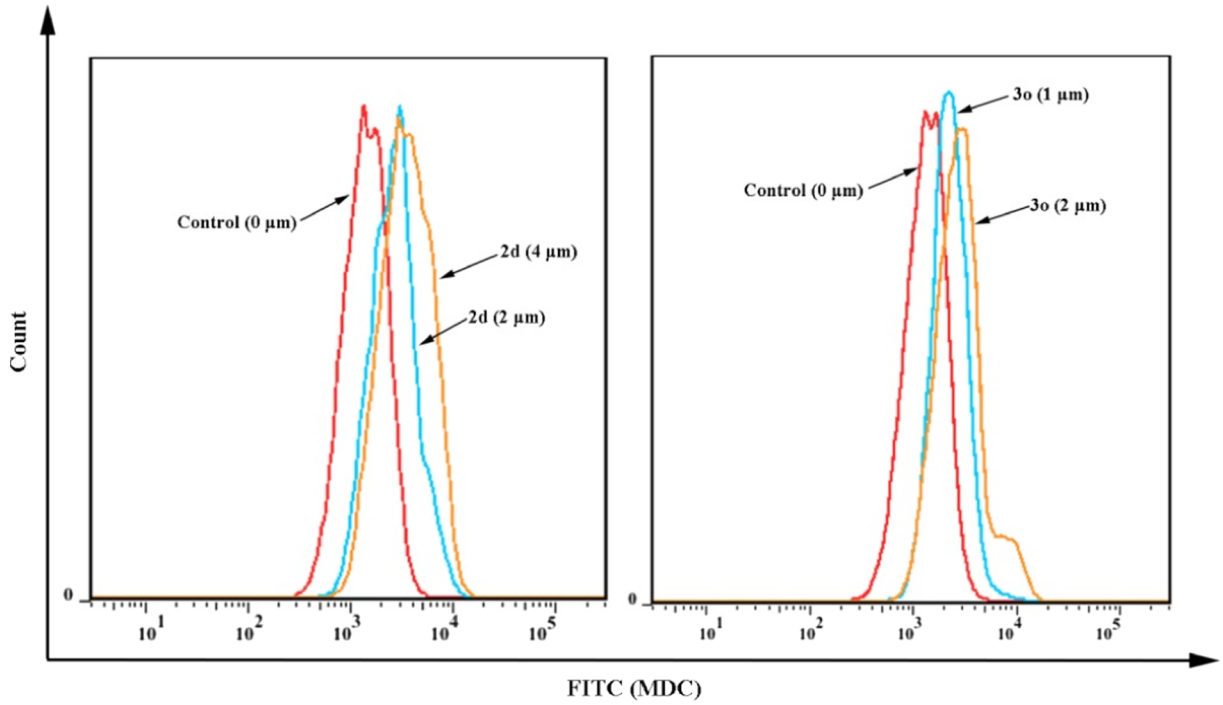


Fig. 7. MDC fluorescent intensity in the autophagy was determined by flow cytometry while HeLa cells were co-incubation with various concentrataions of **2d** (drug concentrations were 0 μM, 2 μM and 4 μM) and **3o** (0 μM, 1 μM and 2 μM) for 48 h. The experiments were done three times and the results of representative experiments were displayed.

(m, 1H, H-19), 1.63 (m, 1H, H-16′), 1.60 (m, 1H, H-15), 1.57–1.59 (m, 2H, H-2 and H-2′), 1.54 (m, 1H, H-22′), 1.52 (m, 1H, H-6), 1.50 (m, 1H, H-9), 1.47 (m, 1H, H-6′), 1.43 (m, 1H, H-7), 1.39 (m, 1H, H-21), 1.36 (m, 1H, H-21′), 1.23 (m, 1H, H-7′), 1.19 (m, 1H, H-19′), 1.14 (s, 3H, H-27), 1.07 (m, 1H, H-1′), 1.03 (m, 1H, H-15′), 1.00 (s, 3H, H-30), 1.94 (s, 3H, H-29), 0.92 (m, 3H, H-23), 0.90 (s, 3H, H-25), 0.80 (s, 3H, H-24), 0.74 (m, 1H, H-5), 0.60 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) *δ*: 177.3, 143.5, 135.7, 132.7, 130.2, 129.5, 127.4, 123.6, 122.6, 78.9, 65.6, 55.2, 47.6, 46.9, 45.9, 41.7, 41.4, 39.3, 38.7, 38.5, 37.0, 33.9, 33.2, 32.7, 32.5, 30.7, 28.2, 27.2, 25.9, 23.7, 23.4, 23.1, 18.3, 16.9, 15.7. HRMS (ES +) *m/z* calcd for $C_{37}H_{54}Br_1O_3$ $[M + H]^+$: 625.3251, found 625.3182.

*4.2.1.4. 2-Methylbenzyl 3beta-hydroxyolean-12-en-28-oate **(2d)***. White solid, yield 86%, mp 185.5–187.6 °C. ^{1}H NMR ($CDCl_3$) *δ*: 7.34– 7.37 (m, 2H), 7.19–7.24 (m, 2H), 5.29 (s, 2H, Ph-**H**$_2$), 5.10 (m, 1H, H-12), 3.21 (dd, 1H, H-3, *J* = 10.6, 5.0 Hz), 2.92 (dd, 1H, H-18, *J* = 13.9, 4.5 Hz), 2.00 (m, 1H, H-16), 1.85 (dd, 2H, H-11 and H-11′, *J* = 8.9, 3.7 Hz), 1.75 (m, 1H, H-22), 1.68 (m, 1H, H-1), 1.66 (m, 1H, H-19), 1.63 (m, 1H, H-16′), 1.60 (m, 1H, H-15), 1.54–1.55 (m, 2H, H-2 and H-2′), 1.52 (m, 1H, H-22′), 1.50 (m, 1H, H-6), 1.47 (m, 1H, H-9), 1.45 (m, 1H, H-6′), 1.43 (m, 1H, H-7), 1.39 (m, 1H, H-21), 1.36 (m, 1H, H-21′), 1.22 (m, 1H, H-7′), 1.16 (m, 1H, H-19′), 1.14 (s, 3H, H-27), 1.07 (m, 1H, H-1′), 1.02 (m, 1H, H-15′), 1.00 (s, 3H, H-30), 0.94 (s, 3H, H-29), 0.92 (m, 3H, H-23), 0.89 (s, 3H, H-25), 0.80 (s, 3H, H-24), 0.72 (m, 1H, H-5), 0.60 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) *δ*: 177.4, 143.6, 136.8, 134.3, 130.2, 129.2, 128.2, 125.9, 122.6, 78.9, 64.5, 55.3, 47.6, 46.9, 45.9, 41.7, 41.4, 39.3, 38.8, 38.5, 37.0, 33.9, 33.2, 32.8, 32.5, 30.7, 28.2, 27.2, 25.9, 23.7, 23.4, 23.1, 18.4, 16.9, 15.7. HRMS (ES +) *m/z* calcd for $C_{38}H_{57}O_3$ $[M + H]^+$: 561.4301, found 561.3742.

*4.2.1.5. 2-Fluorobenzyl 3beta-hydroxy-11-oxo-olean-12-en-30-oate **(4a)***. White solid, yield 87%, mp 187.1–188.2 °C. ^{1}H NMR ($CDCl_3$) δ: 7.32–7.42 (m, 1H), 7.09–7.19 (m, 1H), 5.54 (s, 1H, H-12), 5.31 (s, 2H, Ph-C**H**$_2$), 3.23 (dd, 1H, H-3, *J* = 10.8, 5.5 Hz), 2.79 (dt, 1H, H-1, *J* = 13.4, 3.6 Hz), 2.32 (s, 1H, H-9), 2.06 (m, 1H, H-18), 2.03 (m, 1H, H-15), 1.94 (m, 1H, H-21), 1.91 (m, 1H, H-19), 1.82 (m, 1H, H-16), 1.75 (m, 1H, H-2), 1.71 (m, 1H, H-7), 1.66 (m, 1H, H-2′), 1.62 (m, 1H, H-19′), 1.59 (m, 1H, H-6), 1.50 (m, 1H, H-6′), 1.46 (m, 1H, H-7′), 1.42 (m, 1H, H-22), 1.35 (s, 3H, H-27), 1.33 (m, 1H, H-22′), 1.30 (m, 1H, H-21′), 1.27 (m, 1H, H-16′), 1.17 (s, 3H, H-25), 1.15 (s, 3H, H-28), 1.12 (s, 3H, H-26), 1.01 (s, 3H, H-23), 0.97 (m, 1H, H-1′), 0.96 (m, 1H, H-15′), 0.82 (s, 3H, H-24), 0.76 (s, 3H, H-29), 0.72 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$) δ: 200.1, 176.1, 169.0, 130.7, 130.4, 130.4, 128.5, 124.2, 115.7, 115.5, 78.7, 61.8, 60.4, 54.9, 53.4, 48.2, 45.4, 44.1, 43.2, 41.0, 39.1, 37.6, 37.1, 32.8, 31.8, 31.2, 28.4, 28.3, 28.1, 27.3, 26.5, 26.4, 23.3, 18.7, 17.5, 16.4, 15.6. HRMS (ES+) *m/z* calcd for $C_{37}H_{52}F_1O_4$ $[M + H]^+$: 579.3844, found 579.3846.

*4.2.1.6. 2-Chlorobenzyl 3beta-hydroxy-11-oxo-olean-12-en-30-oate **(4b)***. White solid, yield 89%, mp 94.5–96.6 °C. ^{1}H NMR ($CDCl_3$) δ: 7.40–7.45 (m, 1H), 7.28–7.31 (m, 1H), 5.55 (s, 1H, H-12), 5.31 (s, 2H, Ph-C**H**$_2$), 3.23 (ddd, 1H, H-3, *J* = 10.6, 5.0, 1.8 Hz), 2.84 (m, 1H, H-1), 2.32 (s, 1H, H-9), 2.07 (m, 1H, H-18), 2.03 (m, 1H, H-15), 1.95 (m, 1H, H-21), 1.92 (m, 1H, H-19), 1.82 (m, 1H, H-16), 1.78 (m, 1H, H-2), 1.70 (m, 1H, H-7), 1.67 (m, 1H, H-2′), 1.62 (m, 1H, H-19′), 1.59 (m, 1H, H-6), 1.51 (m, 1H, H-6′), 1.48 (m, 1H, H-7′), 1.45 (m, 1H, H-22), 1.36 (s, 3H, H-27), 1.32 (m, 1H, H-22′), 1.26 (m, 1H, H-21′), 1.21 (m, 1H, H-16′), 1.19 (s, 3H, H-25), 1.12 (s, 3H, H-28), 1.11 (s, 3H, H-26), 1.01 (s, 3H, H-23), 0.99 (m, 1H, H-1′), 0.97 (m, 1H, H-15′), 0.81 (s, 3H, H-24), 0.77 (s, 3H, H-29), 0.70 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$) δ: 200.2, 176.1, 169.0, 133.8, 133.7, 130.2, 129.7, 129.7, 128.5, 127.0, 78.8, 63.8, 61.8, 54.9, 53.5, 48.2, 45.4, 44.2, 43.2, 41.0, 39.1, 37.7, 37.1, 36.57, 32.8, 31.9, 31.8, 31.2, 28.4, 28.4, 28.1, 27.2, 26.5, 26.4, 23.4, 18.7, 17.5, 16.4, 15.6. HRMS (ES +) *m/z* calcd for $C_{37}H_{52}Cl_1O_4$ $[M + H]^+$: 595.3548, found 595.3561.

*4.2.1.7. 2-Bromobenzyl 3beta-hydroxy-11-oxo-olean-12-en-30-oate **(4c)***. White solid, yield 88%, mp 193.1–194.2 °C. ^{1}H NMR ($CDCl_3$) δ: 7.52 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.37 (d, 1H, *J* = 6.4 Hz), 7.29 (td, 1H, *J* = 7.5, 1.2 Hz), 7.14 (td, 1H, *J* = 7.7, 1.8 Hz), 5.51 (s, 1H, H-12), 5.23 (s, 2H, Ph-C**H**$_2$), 3.16 (dd, 1H, H-3, *J* = 11.2, 5.5 Hz), 2.72 (dt, 1H, H-1, *J* = 13.3, 3.5 Hz), 2.26 (s, 1H, H-9), 2.06 (m, 1H, H-18), 2.03 (m, 1H,

H-15), 1.95 (m, 1H, H-21), 1.92 (m, 1H, H-19), 1.87 (m, 1H, H-16), 1.75 (m, 1H, H-2), 1.72 (m, 1H, H-7), 1.65 (m, 1H, H-2′), 1.62 (m, 1H, H-19′), 1.58 (m, 1H, H-6), 1.52 (m, 1H, H-6′), 1.45 (m, 1H, H-7′), 1.41 (m, 1H, H-22), 1.35 (m, 1H, H-22′), 1.30 (s, 3H, H-27), 1.27 (m, 1H, H-21′), 1.20 (m, 1H, H-16′), 1.14 (s, 3H, H-25), 1.07 (s, 3H, H-28), 1.04 (s, 3H, H-26), 0.95 (s, 3H, H-23), 0.90 (m, 1H, H-1′), 0.88 (m, 1H, H-15′), 0.75 (s, 3H, H-24), 0.71 (s, 3H, H-29), 0.64 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$) δ: 200.1, 175.9, 169.0, 135.3, 132.9, 130.1, 129.9, 128.5, 127.6, 123.5, 78.5, 65.9, 61.7, 54.9, 48.1, 45.3, 44.1, 43.1, 41.0, 39.1, 37.7, 37.0, 32.7, 31.8, 31.1, 28.4, 28.2, 27.2, 26.4, 26.4, 23.4, 18.7, 17.5, 16.4, 15.7. HRMS (ES+) *m/z* calcd for $C_{37}H_{52}Br_1O_4$ $[M + H]^+$: 639.3044, found 639.3045.

4.2.1.8. 2-Methylbenzyl 3beta-hydroxy-11-oxo-olean-12-en-30-oate ***(4d)***. White solid, yield 88%, mp 184.5–185.6 °C. ^{1}H NMR ($CDCl_3$) δ: 7.34 (dd, 1H, *J* = 7.5, 1.9 Hz), 7.17 –7.28 (m, 3H), 5.55 (s, 1H, H-12), 5.29 (s, 2H, Ph-C**H**$_2$), 3.23 (dd, 1H, H-3, *J* = 11.0, 5.3 Hz), 2.79 (dt, 1H, H-1, *J* = 13.4, 3.6 Hz), 2.32 (s, 1H, H-9), 2.07 (m, 1H, H-18), 2.04 (m, 1H, H-15), 1.96 (m, 1H, H-21), 1.92 (m, 1H, H-19), 1.81 (m, 1H, H-16), 1.77 (m, 1H, H-2), 1.72 (m, 1H, H-7), 1.65 (m, 1H, H-2′), 1.62 (m, 1H, H-19′), 1.59 (m, 1H, H-6), 1.51 (m, 1H, H-6′), 1.45 (m, 1H, H-7′), 1.42 (m, 1H, H-22), 1.36 (s, 3H, H-27), 1.32 (m, 1H, H-22′), 1.29 (m, 1H, H-21′), 1.26 (m, 1H, H-16′), 1.17 (s, 3H, H-25), 1.14 (s, 3H, H-28), 1.11 (s, 3H, H-26), 1.01 (s, 3H, H-23), 0.97 (m, 1H, H-1′), 0.95 (m, 1H, H-15′), 0.81 (s, 3H, H-24), 0.76 (s, 3H, H-29), 0.72 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$) δ: 200.1, 176.2, 169.0, 136.7, 134.0, 130.4, 129.1, 128.5, 126.1, 78.7, 64.6, 61.8, 54.9, 48.2, 45.4, 44.1, 43.2, 41.1, 39.1, 37.7, 37.1, 32.8, 31.8, 31.2, 28.5, 28.3, 28.1, 27.3, 26.5, 26.4, 23.4, 19.0, 18.7, 17.5, 16.4, 15.6. HRMS (ES +) *m/z* calcd for $C_{38}H_{55}O_4$ $[M + H]^+$: 575.4095, found 575.4106.

4.2.2. General experimental way for the synthesis of 3a-p and 5a-q

To a solution of EDCI (1 mmol) and the corresponding cinnamic acids (1 mmol) in anhydrous dichloromethane (15 mL) at 0 °C, and meanwhile, **2a-d** or **4a-d** was dissolved (1 mmol) in dry dichloromethane (15 mL) at 25 °C. The two mixtures were stirred for 1 h and mixed them. DMAP (0.2 mmol) was added and the mixture was stirred at 25 °C for one day. When the reaction was finish, 1 M HCl was used to wash the mixture and removed the solvent. And purification by column chromatography (petroleum/ethyl acetate = 4/1) to obtain compounds **3a-p** and **5a-q**.

4.2.2.1. 2-Fluorobenzyl 3beta-cinnamoyloxyolean-12-en-28-oate ***(3a)***. White solid, yield 28%, mp 155.7–157.6 °C. ^{1}H NMR ($CDCl_3$) *δ*: 7.69 (d, 1H, *J* = 16.0 Hz), 7.55 (m, 2H), 7.28–7.40 (m, 6H), 7.10 (m, 1H), 6.47 (d, 1H, *J* = 16.0 Hz), 5.32 (s, 2H, Ph-**H**$_2$), 5.16 (d, 1H, H-12, *J* = 13.6 Hz), 4.66 (t, 1H, H-3, *J* = 6.8 Hz), 2.95 (dd, 1H, H-18, *J* = 13.6, 3.6 Hz), 2.04 (m, 1H, H-16), 1.88 (m, 1H, H-11), 1.77 (m, 1H, H-22), 1.73 (m, 1H, H-11′), 1.68 (m, 1H, H-1), 1.65 (m, 1H, H-19), 1.64 (m, 1H, H-16′), 1.58 (m, 1H, H-15), 1.55–1.57 (m, 2H, H-2 and H-2′), 1.54 (m, 1H, H-22′), 1.52 (m, 1H, H-6), 1.49 (m, 1H, H-9), 1.45 (m, 1H, H-6′), 1.42 (m, 1H, H-7), 1.40 (m, 1H, H-21), 1.33 (m, 1H, H-21′), 1.22 (m, 1H, H-7′), 1.19 (m, 1H, H-19′), 1.16 (s, 3H, H-27), 1.04 (m, 1H, H-1′), 1.02 (m, 1H, H-15′), 0.96 (s, 6H, H-29 and H-30), 0.95 (m, 3H, H-23), 0.93 (s, 3H, H-25), 0.92 (s, 3H, H-24), 0.86 (m, 1H, H-5), 0.62 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) *δ*: 177.4, 166.8, 144.3, 143.6, 134.5, 130.6, 130.6, 130.14, 129.9, 128.9, 128.9, 128.0, 128.0, 124.0, 122.5, 118.8, 115.5, 115.2, 81.0, 60.0, 55.3, 47.5, 46.8, 45.8, 41.7, 41.4, 39.3, 38.2, 37.9, 36.9, 33.9, 33.1, 32.7, 32.3, 30.7, 28.1, 27.6, 25.8, 23.6, 23.4, 23.0, 18.2, 16.9, 15.4. HRMS (ES +) *m/z* calcd for $C_{46}H_{60}FO_4$ $[M + H]^+$: 695.4470, found 695.4402.

4.2.2.2. 2-Chlorobenzyl 3beta-cinnamoyloxyolean-12-en-28-oate ***(3b)***. White solid, yield 4%, mp 173.8–176.2 °C. ^{1}H NMR ($CDCl_3$) *δ*: 7.69 (d, 1H, *J* = 16.0 Hz), 7.56 (m, 1H), 7.48–7.50 (m, 2H), 7.40–7.44 (m, 2H), 7.27–7.31 (m, 4H), 6.47 (d, 1H, *J* = 16.0 Hz), 5.32 (s, 2H, Ph-**H**$_2$), 5.19 (m, 1H, H-12), 4.73 (m, 1H, H-3), 2.96 (dd, 1H, H-18, *J* = 13.9, 4.5 Hz), 2.06 (m, 1H, H-16), 1.89 (m, 1H, H-11), 1.75 (m, 1H, H-22), 1.72 (m, 1H, H-11′), 1.69 (m, 1H, H-1), 1.66 (m, 1H, H-19), 1.64 (m, 1H, H-16′), 1.62 (m, 1H, H-9), 1.59 (m, 1H, H-15), 1.56–1.58 (m, 2H, H-2 and H-2′), 1.54 (m, 1H, H-22′), 1.53 (m, 1H, H-6), 1.49 (m, 1H, H-9), 1.46 (m, 1H, H-6′), 1.43 (m, 1H, H-7), 1.41 (m, 1H, H-21), 1.36 (m, 1H, H-21′), 1.33 (m, 1H, H-21′), 1.28 (m, 1H, H-19′), 1.22 (m, 1H, H-7′), 1.19 (m, 1H, H-19′), 1.17 (s, 3H, H-27), 1.09 (m, 1H, H-1′), 1.07 (m, 1H, H-15′), 0.97 (s, 6H, H-29 and H-30), 0.96 (s, 3H, H-23), 0.94 (s, 6H, H-25 and H-24), 0.89 (m, 1H, H-5), 0.63 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) *δ*: 177.3, 166.8, 144.3, 143.6, 135.0, 130.9, 130.9, 130.2, 129.9, 129.9, 129.9, 129.9, 128.9, 128.1, 127.2, 126.8, 122.5, 118.8, 81.0, 63.5, 55.3, 47.5, 46.9, 45.9, 43.6, 41.7, 41.4, 39.3, 38.2, 38.0, 36.9, 33.9, 33.1, 32.7, 32.4, 30.7, 28.1, 27.6, 25.9, 23.7, 23.4, 23.1, 18.3, 16.9, 15.4. HRMS (ES +) *m/z* calcd for $C_{46}H_{60}Cl_1O_4$ $[M + H]^+$: 711.4174, found 711.4185.

4.2.2.3. 2-Methylbenzyl 3beta-cinnamoyloxyolean-12-en-28-oate ***(3c)***. White solid, yield 49%, mp 173.4–175.1 °C. ^{1}H NMR ($CDCl_3$) *δ*: 7.72 (d, 1H, *J* = 16.0 Hz), 7.56 (dd, 2H, *J* = 6.7, 2.9 Hz), 7.41 (dd, 2H, *J* = 4.8, 2.1 Hz), 7.24–7.40 (m, 2H), 7.17–7.23 (m, 3H), 6.50 (d, 1H, *J* = 16.0 Hz), 5.29 (s, 2H, Ph-**H**$_2$), 5.14 (q, 1H, H-12, *J* = 12.6 Hz), 4.70 (dd, 1H, H-3, *J* = 10.1, 6.2 Hz), 2.97 (dd, 1H, H-18, *J* = 13.9, 4.4 Hz), 2.41 (s, 3H), 2.03 (td, 1H, H-16, *J* = 12.6, 3.5 Hz), 1.90 (dd, 1H, H-11, *J* = 9.0, 3.6 Hz), 1.78 (m, 1H, H-22), 1.75 (m, 1H, H-11′), 1.70 (m, 1H, H-1), 1.67 (m, 1H, H-19), 1.66 (m, 1H, H-16′), 1.63 (m, 1H, H-9), 1.61 (m, 1H, H-15), 1.57–1.59 (m, 2H, H-2 and H-2′), 1.55 (m, 1H, H-22′), 1.53 (m, 1H, H-6), 1.49 (m, 1H, H-9), 1.46 (m, 1H, H-6′), 1.41 (m, 1H, H-7), 1.39 (m, 1H, H-21), 1.35 (m, 1H, H-21′), 1.31 (m, 1H, H-21′), 1.27 (m, 1H, H-19′), 1.24 (m, 1H, H-7′), 1.21 (m, 1H, H-19′), 1.19 (s, 3H, H-27), 1.10 (m, 1H, H-1′), 1.05 (m, 1H, H-15′), 1.00 (s, 3H, H-23), 0.98 (s, 6H, H-29 and H-30), 0.97 (s, 3H, H-24), 0.96 (s, 3H, H-25), 0.91 (m, 1H, H-5), 0.65 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) *δ*: 177.4, 166.8, 144.3, 143.7, 136.9, 134.4, 130.2, 130.2, 129.3, 128.9, 128.9, 128.9, 128.3, 128.1, 128.1, 125.9, 122.5, 118.9, 81.0, 64.5, 55.4, 47.6, 46.9, 45.9, 41.7, 41.4, 39.3, 38.2, 38.0, 37.0, 33.9, 33.2, 32.7, 32.5, 30.8, 28.2, 27.7, 25.9, 23.7, 23.5, 23.2, 19.0, 18.3, 16.9, 15.5. HRMS (ES +) *m/z* calcd for $C_{47}H_{63}O_4$ $[M + H]^+$: 691.4721, found 691.4765.

4.2.2.4. 2-Fluorobenzyl 3beta-(4-methyl) cinnamoyloxyolean-12-en-28-oate ***(3d)***. White solid, yield 2%, mp 140.2–141.9 °C. ^{1}H NMR ($CDCl_3$) *δ*: 7.69 (dd, 1H, *J* = 16.0, 1.7 Hz), 7.43 (ddd, 3H, *J* = 17.3, 8.0, 1.8 Hz), 7.02 – 7.38 (m, 4H), 7.18 (m , 1H), 6.42 (dd, 1H, *J* = 16.0, 1.7 Hz), 5.32 (s, 2H, Ph-**H**$_2$), 5.16 (s, 1H, H-12), 4.65 (m, 1H, H-3), 2.92 (dd, 1H, H-18, *J* = 14.1, 4.3 Hz), 2.39 (s, 3H), 2.02 (m, 1H, H-16), 1.87 (dd, 1H, H-11, *J* = 9.1, 3.5 Hz), 1.76 (m, 1H, H-22), 1.73 (m, 1H, H-11′), 1.67 (m, 1H, H-1), 1.65 (m, 1H, H-19), 1.62 (m, 1H, H-16′), 1.59 (dt, 1H, H-15, *J* = 16.9, 6.7 Hz), 1.54–1.56 (m, 2H, H-2 and H-2′), 1.53 (m, 1H, H-22′), 1.51 (m, 1H, H-6), 1.47 (m, 1H, H-9), 1.46 (m, 1H, H-6′), 1.44 (m, 1H, H-7), 1.40 (m, 1H, H-21), 1.37 (m, 1H, H-21′), 1.25 (m, 1H, H-7′), 1.19 (m, 1H, H-19′), 1.15 (s, 3H, H-27), 1.08 (m, 1H, H-1′), 1.03 (m, 1H, H-15′), 0.95 (s, 9H, H-29, H-30 and H-23), 0.92 (s, 6H, H-25 and H-24), 0.88 (m, 1H, H-5), 0.62 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) *δ*: 177.4, 167.0, 144.3, 143.6, 140.5, 131.8, 130.6, 130.6, 129.9, 129.9, 129.6, 129.6, 128.0, 128.0, 124.0, 122.5, 117.7, 115.5, 80.9, 60.0, 53.3, 47.5, 46.8, 45.87, 41.7, 41.4, 39.3, 38.2, 37.9, 36.9, 33.9, 33.1, 32.3, 30.7, 28.1, 27.6, 25.8, 23.6, 23.4, 23.0, 21.5, 16.9, 16.8, 15.4. HRMS (ES +) *m/z* calcd for $C_{47}H_{62}F_1O_4$ $[M + H]^+$: 709.4626, found 709.2953.

4.2.2.5. 2-Chlorobenzyl 3beta-(4-methyl)cinnamoyloxyolean-12-en-28-oate ***(3e)***. White solid, yield 2%, mp 147.2–149.6 °C. ^{1}H NMR ($CDCl_3$) *δ*: 7.66 (d, 1H, *J* = 16.0 Hz), 7.41–7.50 (m, 3H), 7.25–7.31 (m, 3H), 7.21 (d, 2H, *J* = 7.8 Hz), 6.42 (d, 1H, *J* = 16.0 Hz), 5.32 (s, 2H, Ph-**H**$_2$), 5.21 (m, 1H, H-12), 4.72 (m, 1H, H-3), 2.95 (dd, 1H, H-18, *J* = 13.7, 4.4 Hz), 2.39 (s, 3H), 2.03 (m, 1H, H-16), 1.88 (dd, 1H, H-11, *J* = 8.9, 3.5 Hz), 1.74 (m, 1H, H-22), 1.72 (m, 1H, H-11′), 1.68 (m, 1H, H-1), 1.65 (m, 1H, H-19), 1.64 (m, 1H, H-16′), 1.62 (m, 1H, H-9), 1.59

(m, 1H, H-15), 1.56–1.58 (m, 2H, H-2 and H-2′), 1.54 (m, 1H, H-22′), 1.51 (m, 1H, H-6), 1.48 (m, 1H, H-9), 1.45 (m, 1H, H-6′), 1.43 (m, 1H, H-7), 1.41 (m, 1H, H-21), 1.37 (m, 1H, H-21′), 1.32 (m, 1H, H-21′), 1.29 (m, 1H, H-19′), 1.20 (m, 1H, H-7′), 1.19 (m, 1H, H-19′), 1.16 (s, 3H, H-27), 1.09 (m, 1H, H-1′), 1.07 (m, 1H, H-15′), 0.96 (s, 9H, H-29, H-30 and H-23), 0.93 (s, 6H, H-25 and H-24), 0.88 (m, 1H, H-5), 0.63 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) δ: 177.3, 167.0, 144.3, 143.6, 135.0, 130.9, 130.9, 130.0, 129.9, 129.9, 129.9, 129.9, 129.6, 128.0, 127.2, 126.8, 122.5, 117.7, 80.8, 63.5, 55.3, 47.5, 46.9, 45.9, 43.6, 41.7, 41.4, 39.3, 38.2, 37.9, 36.9, 33.9, 33.1, 32.7, 32.4, 30.7, 28.1, 27.6, 25.9, 23.7, 23.4, 23.1, 21.5, 18.2, 16.9, 15.4. HRMS (ES +) *m/z* calcd for $C_{47}H_{62}Cl_1O_4$ $[M + H]^+$: 725.4331, found 725.3891.

*4.2.2.6. 2-Bromobenzyl 3beta-(4-methyl)cinnamoyloxyolean-12-en-28-oate (**3f**)*. White solid, yield 3%, mp 170.6–172.8 °C. ^{1}H NMR ($CDCl_3$) δ: 7.66 (d, 1H, J = 16.0, 1.7 Hz), 7.58–7.62 (m, 2H), 7.44–7.52 (m, 2H), 7.31–7.37 (m , 2H), 7.18–7.24 (m, 2H), 6.41 (d, 1H, J = 16.0 Hz), 5.32 (s, 2H, Ph-**H**$_2$), 5.15 (m, 1H, H-12), 4.65 (m, 1H, H-3), 2.96 (dd, 1H, H-18, J = 14.1, 4.3 Hz), 2.39 (s, 3H), 2.02 (td, 1H, H-16, J = 13.2, 3.9 Hz), 1.88 (dd, 1H, H-11, J = 8.8, 3.7 Hz), 1.78 (m, 1H, H-22), 1.73 (m, 1H, H-11′), 1.67 (m, 1H, H-1), 1.65 (m, 1H, H-19), 1.62 (m, 1H, H-16′), 1.58 (m, 1H, H-15), 1.54–1.56 (m, 2H, H-2 and H-2′), 1.53 (m, 1H, H-22′), 1.51 (m, 1H, H-6), 1.48 (m, 1H, H-9), 1.45 (m, 1H, H-6′), 1.42 (m, 1H, H-7), 1.40 (m, 1H, H-21), 1.38 (m, 1H, H-21′), 1.27 (m, 1H, H-7′), 1.21 (m, 1H, H-19′), 1.16 (s, 3H, H-27), 1.08 (m, 1H, H-1′), 1.03 (m, 1H, H-15′), 0.96 (s, 6H, H-30 and 29), 0.95 (s, 3H, H-23), 0.93 (s, 6H, H-25 and H-24), 0.86 (m, 1H, H-5), 0.62 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) δ: 177.3, 167.0, 144.3, 143.6, 135.7, 133.2, 132.7, 130.9, 130.2, 129.6, 129.6, 129.5, 128.0, 128.0, 127.9, 127.4, 122.5, 117.7, 80.8, 65.6, 55.3, 47.5, 47.0, 45.9, 41.7, 41.4, 39.3, 38.2, 37.9, 36.9, 33.9, 33.1, 32.7, 32.45 , 30.7, 29.7, 28.1, 27.7, 25.9, 23.7, 23.4, 23.1, 21.5, 18.2, 16.9, 15.4. HRMS (ES +) *m/z* calcd for $C_{47}H_{62}Br_1O_4$ $[M + H]^+$: 769.3826, found 769.3841.

*4.2.2.7. 2-Methylbenzyl 3beta-(4-methyl)cinnamoyloxyolean-12-en-28-oate (**3g**)*. White solid, yield 6%, mp 191.2–192.6 °C. ^{1}H NMR ($CDCl_3$) δ: 7.68 (d, 1H, J = 16.0 Hz), 7.47 (d, 2H, J = 7.9 Hz), 7.35 (d, 2H, J = 8.0 Hz), 7.22–7.27 (m, 4H), 6.43 (d, 1H, J = 8.0 Hz), 5.32 (s, 2H, Ph-**H**$_2$), 5.14 (q, 1H, H-12, J = 10.4 Hz), 4.68 (dd, 1H, H-3, J = 9.9, 6.5 Hz), 2.96 (dd, 1H, H-18, J = 13.8, 4.4 Hz), 2.47 (s, 3H), 2.03 (td, 1H, H-16, J = 12.5, 3.5 Hz), 1.90 (dd, 1H, H-11, J = 8.9, 3.6 Hz), 1.78 (m, 1H, H-22), 1.74 (m, 1H, H-11′), 1.70 (m, 1H, H-1), 1.67 (m, 1H, H-19), 1.66 (m, 1H, H-16′), 1.63 (m, 1H, H-9), 1.60 (m, 1H, H-15), 1.57–1.59 (m, 2H, H-2 and H-2′), 1.55 (m, 1H, H-22′), 1.53 (m, 1H, H-6), 1.49 (m, 1H, H-9), 1.46 (m, 1H, H-6′), 1.41 (m, 1H, H-7), 1.39 (m, 1H, H-21), 1.35 (m, 1H, H-21′), 1.31 (m, 1H, H-21′), 1.27 (m, 1H, H-19′), 1.24 (m, 1H, H-7′), 1.20 (m, 1H, H-19′), 1.18 (s, 3H, H-27), 1.10 (m, 1H, H-1′), 1.05 (m, 1H, H-15′), 0.99 (s, 3H, H-23), 0.98 (s, 6H, H-29 and H-30), 0.96 (s, 3H, H-24 and H-25), 0.90 (m, 1H, H-5), 0.64 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) δ: 177.4, 167.0, 144.3, 143.7, 140.5, 137.2, 135.5, 130.7, 129.8, 129.8, 129.0, 129.0, 128.2, 128.1, 126.4, 125.9, 122.5, 117.8, 80.9, 64.5, 55.4, 47.6, 46.9, 45.9, 41.7, 41.4, 39.3, 38.2, 38.0, 37.0, 33.9, 33.1, 32.7, 32.5, 30.7, 28.2, 27.6, 25.9, 23.7, 23.4, 23.1, 21.5, 19.0, 18.3, 16.9, 15.4. HRMS (ES +) *m/z* calcd for $C_{48}H_{65}O_4$ $[M + H]^+$: 705.4877, found 705.4717.

*4.2.2.8. 2-Fluorobenzyl 3beta-(4-fluoro)cinnamoyloxyolean-12-en-28-oate (**3h**)*. White solid, yield 14%, mp 156.1–158.2 °C. ^{1}H NMR ($CDCl_3$) δ: 7.64 (d, 1H, J = 16.0 Hz), 7.52–7.55 (m , 2H), 7.28–7.40 (m, 5H), 7.10 (m , 1H), 6.38 (d, 1H, J = 16.0 Hz), 5.32 (s, 2H, Ph-**H**$_2$), 5.16 (t, 1H, H-12, J = 1.3 Hz), 4.66 (m, 1H, H-3), 2.92 (dd, 1H, H-18, J = 13.8, 4.5 Hz), 2.00 (m, 1H, H-16), 1.87 (dd, 1H, H-11, J = 8.9, 3.6 Hz), 1.77 (m, 1H, H-22), 1.71 (m, 1H, H-11′), 1.68 (m, 1H, H-1), 1.65 (m, 1H, H-19), 1.62 (m, 1H, H-16′), 1.58 (m, 1H, H-15), 1.55–1.57 (m, 2H, H-2 and H-2′), 1.54 (m, 1H, H-22′), 1.51 (m, 1H, H-6), 1.48 (m, 1H, H-9), 1.45 (m, 1H, H-6′), 1.42 (m, 1H, H-7), 1.40 (m, 1H, H-21), 1.33 (m, 1H, H-21′), 1.23 (m, 1H, H-7′), 1.19 (m, 1H, H-19′), 1.15 (s, 3H, H-27), 1.08 (m, 1H, H-1′), 1.05 (m, 1H, H-15′), 0.95 (s, 9H, H-29 , H-30 and H-23), 0.92 (s, 6H, H-25 and H-24), 0.88 (m, 1H, H-5), 0.62 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) δ: 177.4, 166.7, 162.6, 159.8, 143.6, 143.0, 130.6, 130.6, 129.9, 129.9, 129.9, 124.0, 122.4, 118.6, 116.1, 115.9, 115.5, 115.2, 81.1, 60.1, 55.3, 47.5, 46.8, 45.8, 41.7, 41.4, 39.3, 38.1, 37.9, 36.9, 33.9, 33.1, 32.7, 32.3, 30.7, 28.1, 27.6, 25.8, 23.6, 23.4, 23.0, 18.2, 16.9, 15.4. HRMS (ES +) *m/z* calcd for $C_{46}H_{59}F_2O_4$ $[M + H]^+$: 713.4376, found 713.4463.

*4.2.2.9. 2-Chlorobenzyl 3beta-(4-fluoro)cinnamoyloxyolean -12-en-28-oate (**3i**)*. White solid, yield 33%, mp 183.1–185.3 °C. ^{1}H NMR ($CDCl_3$) δ: 7.63 (d, 1H, J = 16.0 Hz), 7.45–7.51 (m, 2H), 7.37 (m, 1H), 7.25–7.27 (m, 3H), 7.06 (t, 2H, J = 8.4 Hz), 6.38 (dd, 1H, J = 16.0, 1.6 Hz), 5.28 (s, 2H, Ph-**H**$_2$), 5.20 (dd, 1H, H-12, J = 11.9, 10.3 Hz), 4.66 (m, 1H, H-3), 2.92 (dd, 1H, H-18, J = 13.9, 4.3 Hz), 2.02 (m, 1H, H-16), 1.87 (m, 1H, H-11), 1.78 (m, 1H, H-22), 1.71 (m, 1H, H-11′), 1.68 (m, 1H, H-1), 1.66 (m, 1H, H-19), 1.62 (m, 1H, H-16′), 1.60 (m, 1H, H-15), 1.56–1.58 (m, 2H, H-2 and H-2′), 1.54 (m, 1H, H-22′), 1.51 (m, 1H, H-6), 1.47 (m, 1H, H-9), 1.43 (m, 1H, H-6′), 1.42 (m, 1H, H-7), 1.41 (m, 1H, H-21), 1.34 (m, 1H, H-21′), 1.22 (m, 1H, H-7′), 1.19 (m, 1H, H-19′), 1.15 (s, 3H, H-27), 1.08 (m, 1H, H-1′, J = 10.1 Hz), 1.05 (m, 1H, H-15′), 0.95 (s, 6H, H-29 and H-30), 0.93 (s, 9H, H-25 ,H-24 and H-23), 0.87 (m, 1H, H-5), 0.62 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) δ: 177.2, 166.6, 162.5, 143.6, 142.9, 134.1, 130.9, 130.1, 129.9, 129. 5, 129.3, 127.2, 126.8, 122.5, 118.6, 116.1, 115.9, 81.1, 63.5, 55.3, 47.6, 46.9, 45.9, 41.7, 41.4, 39.3, 38.1, 37.9, 36.9, 33.9, 33.1, 32.7, 32.5, 30.7, 28.1, 27.6, 25.9, 23.7, 23.4, 23.1, 18.3, 16.9, 15.4. HRMS (ES +) *m/z* calcd for $C_{46}H_{57}Cl_1F_1O_4$ $[M-H]^-$: 727.3935, found 727.3943.

*4.2.2.10. 2-Bromobenzyl 3beta-(4-fluoro)cinnamoyloxyolean-12-en-28-oate (**3j**)*. White solid, yield 16%, mp 152.1–153.5 °C. ^{1}H NMR ($CDCl_3$) δ: 7.59–7.63 (m, 2H), 7.37 (m, 1H), 7.25–7.27 (m, 3H), 7.09 (t, 1H, J = 8.6 Hz), 6.39 (d, 1H, J = 16.0 Hz), 5.32 (s, 2H, Ph-**H**$_2$), 5.15 (m, 1H, H-12), 4.64 (m, 1H, H-3), 2.92 (dd, 1H, H-18, J = 14.0, 4.0 Hz), 2.02 (m, 1H, H-16), 1.87 (dd, 1H, H-11, J = 9.0, 3.6 Hz), 1.78 (m, 1H, H-22), 1.70 (m, 1H, H-11′), 1.68 (m, 1H, H-1), 1.66 (m, 1H, H-19), 1.62 (m, 1H, H-16′), 1.60 (m, 1H, H-15), 1.56–1.58 (m, 2H, H-2 and H-2′), 1.54 (m, 1H, H-22′), 1.52 (m, 1H, H-6), 1.47 (m, 1H, H-9), 1.45 (m, 1H, H-6′), 1.42 (m, 1H, H-7), 1.40 (m, 1H, H-21), 1.34 (m, 1H, H-21′), 1.25 (m, 1H, H-7′), 1.20 (m, 1H, H-19′), 1.16 (s, 3H, H-27), 1.10 (m, 1H, H-1′, J = 10.1 Hz), 1.07 (m, 1H, H-15′), 0.97 (s, 3H, H-23), 0.96 (s, 6H, H-29, H-30), 0.93 (s, 6H, H-25, H-24), 0.89 (m, 1H, H-5), 0.63 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) δ: 177.3, 166.7, 162.6, 143.6, 143.0, 133.2, 132.7, 130.9, 130.2, 130.1, 129.9, 129.8, 129.5, 127.9, 127.4, 118.6, 116.1, 115.9, 81.0, 65.6, 55.3, 47.5, 46.9, 45.9, 41.7, 41.4, 39.3, 38.1, 37.9, 36.9, 33.9, 33.1, 32.6, 32.4, 30.7, 28.1, 27.6, 25.9, 23.6, 23.4, 23.1, 18.2, 16.9, 15.4. HRMS (ES +) *m/z* calcd for $C_{46}H_{59}Br_1F_1O_4$ $[M + H]^+$: 773.3576, found 773.3581.

*4.2.2.11. 2-Methylbenzyl 3beta-(4-fluoro)cinnamoyloxyolean-12-en-28-oate (**3k**)*. White solid, yield 33%, mp 159.7–161.2 °C. ^{1}H NMR ($CDCl_3$) δ: 7.67 (d, 1H, J = 16.0 Hz), 7.54 (t, 2H, J = 6.6 Hz), 7.36 (dd, 1H, J = 18.7, 7.3 Hz), 7.25 (d, 2H, J = 15.0 Hz), 7.21 (d, 2H, J = 7.0 Hz), 7.09 (t, 1H, J = 8.4 Hz), 6.40 (d, 1H, J = 16.0 Hz), 5.32 (s, 2H, Ph-**H**$_2$), 5.13 (q, 1H, H-12, J = 12.6 Hz), 4.66 (d, 1H, H-3, J = 19.4 Hz), 2.96 (d, 1H, H-18, J = 13.6, 4.4 Hz), 2.40 (s, 3H), 2.03 (t, 1H, H-16, J = 13.8 Hz), 1.89 (d, 1H, H-11, J = 8.8 Hz), 1.80 (m, 1H, H-22), 1.76 (m, 1H, H-11′), 1.72 (m, 1H, H-1), 1.69 (m, 1H, H-19), 1.66 (m, 1H, H-16′), 1.63 (m, 1H, H-9), 1.60 (m, 1H, H-15), 1.56–1.58 (m, 2H, H-2 and H-2′), 1.55 (m, 1H, H-22′), 1.52 (m, 1H, H-6), 1.49 (m, 1H, H-9), 1.45 (m, 1H, H-6′), 1.42 (m, 1H, H-7), 1.39 (m, 1H, H-21), 1.35 (m, 1H, H-21′), 1.31 (m, 1H, H-21′), 1.26 (m, 1H, H-19′), 1.24 (m, 1H, H-7′), 1.22 (m, 1H, H-19′), 1.18 (s, 3H, H-27), 1.10 (m, 1H, H-1′), 1.06 (m, 1H, H-15′), 0.98 (s, 6H, H-29, H-30 and H-23), 0.95 (s, 6H, H-24 and H-25), 0.90 (m, 1H, H-5), 0.64 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) δ:

177.4, 166.6, 162.6, 143.7, 143.0, 136.9, 130.8, 130.7, 130.2, 129.9, 129.2, 128.9, 128.2, 125.9, 122.5, 118.6, 116.1, 115.9, 81.1, 64.5, 55.4, 47.6, 46.9, 45.9, 41.7, 41.4, 39.3, 38.2, 38.0, 37.0, 33.9, 33.2, 32.7, 32.5, 30.7, 28.2, 27.6, 25.9, 23.7, 23.1, 19.0, 18.8, 18.3, 16.90, 15.4. HRMS (ES +) *m/z* calcd for $C_{47}H_{62}F_1O_4$ $[M + H]^+$: 709.4626, found 709.4639.

*4.2.2.12. 2-Fluorobenzyl 3beta-(4-nitro) cinnamoyloxyolean-12-en-28-oate (**3l**)*. White solid, yield 2%, mp 122.3–124.1 °C. ^{1}H NMR ($CDCl_3$) *δ*: 8.26 (d, 2H, *J* = 8.4 Hz), 7.69 (d, 2H, *J* = 8.8 Hz), 7.29–7.46 (t, 3H, *J* = 7.6 Hz), 7.06–7.16 (m, 2H), 6.58 (d, 1H, *J* = 16.1 Hz), 5.32 (s, 2H, Ph-**H**$_2$), 5.16 (s, 1H, H-12), 4.67 (t, 1H, H-3, *J* = 8.1 Hz), 2.92 (d, 1H, H-18, *J* = 14.1 Hz), 2.02 (m, 1H, H-16), 1.88 (d, 1H, H-11, *J* = 9.8, Hz), 1.74 (m, 1H, H-22), 1.72 (m, 1H, H-11′), 1.70 (m, 1H, H-1), 1.66 (m, 1H, H-19), 1.63 (m, 1H, H-16′), 1.58 (m, 1H, H-15), 1.54–1.56 (m, 2H, H-2 and H-2′), 1.53 (m, 1H, H-22′), 1.51 (m, 1H, H-6), 1.47 (m, 1H, H-9), 1.45 (m, 1H, H-6′), 1.44 (m, 1H, H-7), 1.40 (m, 1H, H-21), 1.36 (m, 1H, H-21′), 1.23 (m, 1H, H-7′), 1.19 (m, 1H, H-19′), 1.15 (s, 3H, H-27), 1.10 (m, 1H, H-1′), 1.00 (m, 1H, H-15′), 0.96 (s, 6H, H-29 and H-30), 0.94 (s, 3H, H-23), 0.94 (s, 3H, H-24), 0.92 (s, 3H, H-25), 0.85(m, 1H, H-5), 0.63 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) *δ*: 177.3, 165.8, 148.5, 143.6, 141.3, 140.7, 130.9, 130.6, 129.9, 128.6, 128.6, 124.1, 124.1, 124.0, 123.2, 122.4, 115.4, 115.2, 81.7, 60.0, 55.3, 47.6, 46.8, 45.8, 41.7, 41.4, 39.3, 38.1, 37.9, 36.9, 33.9, 33.1, 32.3, 30.7, 28.1, 27.6, 25.8, 23.6, 23.4, 23.0, 16.9, 16.8, 15.4. HRMS (ES +) *m/z* calcd for $C_{46}H_{59}F_1N_1O_6$ $[M + H]^+$: 740.4321, found 740.4732.

*4.2.2.13. 2-Chlorobenzyl 3beta-(4-nitro) cinnamoyloxyolean-12-en-28-oate (**3m**)*. White solid, yield 3%, mp 97.1–99.6 °C. ^{1}H NMR ($CDCl_3$) *δ*: 8.26 (d, 2H, *J* = 8.0 Hz), 7.71 (d, 2H, *J* = 8.8 Hz), 7.40–7.48 (m, 2H), 7.27–7.28 (m, 3H), 6.58 (d, 1H, *J* = 16.0 Hz), 5.32 (s, 2H, Ph-**H**$_2$), 5.16 (s, 1H, H-12), 4.70 (m, 1H, H-3), 2.92 (dd, 1H, H-18, *J* = 14.2, 4.5 Hz), 2.02 (m, 1H, H-16), 1.88 (dd, 1H, H-11, *J* = 9.0, 3.4 Hz), 1.76 (m, 1H, H-22), 1.74 (m, 1H, H-11′), 1.72 (m, 1H, H-1), 1.68 (m, 1H, H-19), 1.64 (m, 1H, H-16′), 1.61 (m, 1H, H-15), 1.56–1.59 (m, 2H, H-2 and H-2′), 1.53 (m, 1H, H-22′), 1.51 (m, 1H, H-6), 1.47 (m, 1H, H-9), 1.45 (m, 1H, H-6′), 1.44 (m, 1H, H-7), 1.40 (m, 1H, H-21), 1.37 (m, 1H, H-21′), 1.24 (m, 1H, H-7′), 1.19 (m, 1H, H-19′), 1.16 (s, 3H, H-27), 1.07 (m, 1H, H-1′), 1.00 (m, 1H, H-15′), 0.95 (s, 9H, H-29, H-23 and H-30), 0.93 (s, 6H, H-24 and H-25), 0.84 (m, 1H, H-5), 0.63 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) *δ*: 177.3, 165.8, 148.4, 143.7, 141.3, 140.7, 134.1, 133.8, 130.0, 129.5, 129.3, 128.6, 128.6, 126.7, 124.2, 123.2, 123.2, 122.5, 81.7, 63.5, 55.3, 47.5, 46.9, 45.9, 41.7, 41.4, 39.3, 38.1, 37.9, 36.9, 33.9, 33.1, 32.4, 30.7, 28.1, 27.6, 25.9, 23.6, 23.4, 23.1, 18.2, 16.9, 15.4. HRMS (ES +) *m/z* calcd for $C_{46}H_{59}Cl_1N_1O_6$ $[M + H]^+$: 756.4025, found 756.3934.

*4.2.2.14. 2-Bromobenzyl 3beta-(4-nitro) cinnamoyloxyolean-12-en-28-oate (**3n**)*. White solid, yield 12%, mp 216.4–218.5 °C. ^{1}H NMR ($CDCl_3$) *δ*: 8.26 (d, 2H, *J* = 8.3 Hz), 7.68–7.72 (m, 3H), 7.58 (d, 1H, *J* = 8.0 Hz), 7.46 (d, 1H, *J* = 7.7 Hz), 7.29–7.34 (m, 1H), 7.29–7.34 (m, 1H), 6.58 (d, 1H, *J* = 16.0 Hz), 5.32 (s, 2H, Ph-**H**$_2$), 5.16 (q, 1H, H-12, *J* = 13.1 Hz), 4.70 (m, 1H, H-3), 2.95 (d, 1H, H-18, *J* = 13.9 Hz), 2.02 (t, 1H, H-16, *J* = 14.8 Hz), 1.87 (d, 1H, H-11, *J* = 9.1 Hz), 1.81 (m, 1H, H-22), 1.76 (m, 1H, H-11′), 1.72 (m, 1H, H-1), 1.68 (m, 1H, H-19), 1.65 (m, 1H, H-16′), 1.62 (m, 1H, H-15), 1.55–1.58 (m, 2H, H-2 and H-2′), 1.53 (m, 1H, H-22′), 1.51 (m, 1H, H-6), 1.47 (m, 1H, H-9), 1.45 (m, 1H, H-6′), 1.44 (m, 1H, H-7), 1.40 (m, 1H, H-21), 1.37 (m, 1H, H-21′), 1.22 (m, 1H, H-7′), 1.18 (m, 1H, H-19′), 1.16 (s, 3H, H-27), 1.07 (m, 1H, H-1′), 1.00 (m, 1H, H-15′), 0.95 (s, 9H, H-29, H-23 and H-30), 0.93 (s, 6H, H-24 and H-25), 0.88 (m, 1H, H-5), 0.62 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) *δ*: 177.2, 165.8, 148.4, 143.7, 141.3, 140.7, 135.7, 132.7, 130.2, 129.5, 128.6, 128.6, 127.4, 124.1, 124.1, 123.6, 123.2, 122.5, 81.7, 65.6, 55.3, 47.6, 46.9, 45.9, 41.7, 41.4, 39.3, 38.1, 37.9, 36.9, 33.9, 33.1, 32.4, 30.7, 28.1, 27.7, 25.9, 23.6, 23.4, 23.1, 18.2, 16.9, 15.4. HRMS (ES +) *m/z* calcd for $C_{46}H_{58}Br_1N_1O_6$ Na $[M + Na]^+$: 822.3340, found 822.1312.

*4.2.2.15. 2-Methylbenzyl 3beta-(4-nitro) cinnamoyloxyolean-12-en-28-oate (**3o**)*. White solid, yield 2%, mp 89.4–91.2 °C. ^{1}H NMR ($CDCl_3$) *δ*: 8.26 (d, 2H, *J* = 8.4 Hz), 7.66–7.75 (m, 3H), 7.36 (d, 1H, *J* = 7.3 Hz), 7.17–7.29 (m, 3H), 6.58 (d, 1H, *J* = 16.0 Hz), 5.32 (s, 2H, Ph-**H**$_2$), 5.10 (q, 1H, H-12, *J* = 12.8 Hz), 4.70 (m, 1H, H-3), 2.92 (m, 1H, H-18), 2.38 (s, 3H), 2.00 (t, 1H, H-16, *J* = 13.7 Hz), 1.87 (d, 1H, H-11, *J* = 9.4 Hz), 1.81 (m, 1H, H-22), 1.76 (m, 1H, H-11′), 1.72 (m, 1H, H-1), 1.68 (m, 1H, H-19), 1.65 (m, 1H, H-16′), 1.62 (m, 1H, H-15), 1.55–1.58 (m, 2H, H-2 and H-2′), 1.53 (m, 1H, H-22′), 1.51 (m, 1H, H-6), 1.47 (m, 1H, H-9), 1.45 (m, 1H, H-6′), 1.43 (m, 1H, H-7), 1.40 (m, 1H, H-21), 1.36 (m, 1H, H-21′), 1.24 (m, 1H, H-7′), 1.19 (m, 1H, H-19′), 1.15 (s, 3H, H-27), 1.07 (m, 1H, H-1′), 1.03 (m, 1H, H-15′), 0.96 (s, 9H, H-29, H-23 and H-30), 0.94 (s, 6H, H-24 and H-25), 0.88 (m, 1H, H-5), 0.61 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) *δ*: 177.4, 165.8, 143.7, 141.3, 141.2, 140.7, 140.2, 136.9, 134.3, 130.2, 129.2, 128.6, 128.2, 125.9, 124.1, 123.2, 122.4, 81.7, 64.4, 55.3, 47.6, 46.9, 45.9, 41.7, 41.4, 39.3, 38.1, 37.9, 36.9, 33.9, 33.1, 32.4, 30.7, 28.1, 27.6, 25.8, 23.6, 23.4, 23.1, 18.9, 18.2, 16.9, 15.4. HRMS (ES +) *m/z* calcd for $C_{47}H_{60}N_1O_6$ $[M-H]^-$: 734.4426, found 734.3986.

*4.2.2.16. 2-Fluorobenzyl 3beta-(2, 3, 4, 5, 6-Pentafluoro) cinnamoyloxyolean −12-en-28-oate (**3p**)*. White solid, yield 48%, mp 168.2–169.3 °C. ^{1}H NMR ($CDCl_3$) *δ*: 7.62 (t, 1H, *J* = 17.0 Hz), 7.39 (p, 1H, *J* = 7.8 Hz), 7.27 (d, 1H, *J* = 9.4 Hz), 7.06 (dq, 3H, *J* = 27.5, 9.5, 9.0 Hz), 6.38 (t, 1H, *J* = 17.0 Hz), 5.28 (d, 2H, Ph-**H**$_2$, *J* = 16.7 Hz), 5.13 (d, 1H, H-12, *J* = 16.2 Hz), 4.63 (td, 1H, H-3, *J* = 12.4, 12.0, 6.7 Hz), 2.92 (t, 1H, H-18, *J* = 9.2 Hz), 2.22 (m, 1H, H-16), 1.85 (q, 1H, H-11, *J* = 8.9, 8.4 Hz), 1.77 (m, 1H, H-22), 1.71 (m, 1H, H-11′), 1.68 (m, 1H, H-1), 1.65 (m, 1H, H-19), 1.62 (m, 1H, H-16′), 1.58 (m, 1H, H-15), 1.55–1.57 (m, 2H, H-2 and H-2′), 1.54 (m, 1H, H-22′), 1.51 (m, 1H, H-6), 1.48 (m, 1H, H-9), 1.45 (m, 1H, H-6′), 1.42 (m, 1H, H-7), 1.40 (m, 1H, H-21), 1.33 (m, 1H, H-21′), 1.23 (m, 1H, H-7′), 1.19 (m, 1H, H-19′), 1.16 (s, 3H, H-27), 1.08 (m, 1H, H-1′), 1.05 (m, 1H, H-15′), 0.95 (s, 3H, H-23), 0.92 (s, 9H, H-29 and H-30), 0.91 (s, 6H, H-25 and H-24), 0.78 (m, 1H, H-5), 0.62 (s, 3H, H-26); ^{13}C NMR ($CDCl_3$) *δ*: 177.2, 165.7, 162.2, 159.7, 143.6, 130.6, 130.5, 129.9, 129.8, 127.7, 126.9, 124.0, 123.9, 123.7, 123.5, 122.4, 115.4, 115.2, 81.8, 60.0, 55.3, 47.5, 46.8, 45.8, 41.6, 41.4, 39.3, 38.1, 37.9, 36.9, 33.8, 33.1, 32.3, 30.7, 28.1, 27.6, 25.8, 23.6, 23.4, 23.0, 18.2, 16.8, 15.3. HRMS (ES +) *m/z* calcd for $C_{46}H_{55}F_6O_4$ $[M + H]^+$: 785.3999, found 785.4045.

*4.2.2.17. 2-Fluorobenzyl 3beta-cinnamoyloxy-11-oxo-olean-12-en-30-oate (**5a**)*. White solid, yield 31%, mp 169.1–171.4 °C. ^{1}H NMR ($CDCl_3$) δ: 7.68 (d, 1H, *J* = 16.0 Hz), 7.55 (dt, 2H, *J* = 5.9, 3.6 Hz), 7.30 –7.46 (m, 5H), 7.07–7.22 (m, 2H), 6.46 (d, 1H, *J* = 16.0 Hz), 5.56 (s, 1H, H-12), 5.31 (s, 2H, Ph-C**H**$_2$), 4.68 (dd, 1H, H-3, *J* = 11.6, 4.8 Hz), 2.84 (dt, 1H, H-1, *J* = 13.4, 3.6 Hz), 2.38 (s, 1H, H-9), 2.08 (m, 1H, H-18), 2.03 (m, 1H, H-15), 1.96 (m, 1H, H-21), 1.92 (m, 1H, H-19), 1.82 (m, 1H, H-16), 1.75 (m, 1H, H-2), 1.71 (m, 1H, H-7), 1.67 (m, 1H, H-2′), 1.61 (m, 1H, H-19′), 1.57 (m, 1H, H-6), 1.49 (m, 1H, H-6′), 1.44 (m, 1H, H-7′), 1.41 (m, 1H, H-22), 1.37 (s, 3H, H-27), 1.34 (m, 1H, H-22′), 1.32 (m, 1H, H-21′), 1.27 (m, 1H, H-16′), 1.21 (s, 3H, H-25), 1.18 (s, 3H, H-28), 1.14 (s, 3H, H-26), 1.10 (m, 1H, H-1′), 1.04 (m, 1H, H-15′), 0.97 (s, 3H, H-23), 0.94 (s, 3H, H-24), 0.87 (m, 1H, H-5), 0.77 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 200.0, 176.1, 169.0, 166.8, 159.8, 144.3, 134.5, 130.8, 130.5, 130.4, 130.2, 128.9, 128.9, 128.5, 128.0, 128.0, 124.2, 118.8, 115.5, 80.7, 61.7, 60.4, 55.0, 53.5, 48.2, 45.4, 44.1, 43.2, 41.0, 38.8, 38.3, 37.6, 36.9, 32.7, 31.8, 31.2, 29.7, 28.4, 28.3, 28.1, 26.5, 26.4, 23.7, 23.3, 18.7, 17.4, 16.9, 16.5. HRMS (ES +) *m/z* calcd for $C_{46}H_{58}F_1O_5$ $[M + H]^+$: 709.4263, found 709.4271.

*4.2.2.18. 2-Chlorobenzyl 3beta-cinnamoyloxy-11-oxo-olean-12-en-30-oate (**5b**)*. White solid, yield 11%, mp 181.3–182.7 °C. ^{1}H NMR ($CDCl_3$) δ: 7.69 (dd, 1H, *J* = 16.0, 1.4 Hz), 7.51–7.62 (m, 2H),

7.37–7.50 (m, 5H), 7.26–7.41 (m, 2H), 6.46 (d, 1H, J = 16.0 Hz), 5.57 (s, 1H, H-12), 5.32 (s, 2H, Ph-C**H**$_2$), 4.69 (m, 1H, H-3), 2.84 (m, 1H, H-1), 2.39 (s, 1H, H-9), 2.10 (m, 1H, H-18), 2.06 (m, 1H, H-15), 1.96 (m, 1H, H-21), 1.92 (m, 1H, H-19), 1.84 (m, 1H, H-16, J = 13.2, 6.7 Hz), 1.76 (m, 1H, H-2), 1.72 (m, 1H, H-7), 1.68 (m, 1H, H-2′), 1.61 (m, 1H, H-19′), 1.53 (m, 1H, H-6), 1.47 (m, 1H, H-6′), 1.45 (m, 1H, H-7′), 1.41 (m, 1H, H-22), 1.39 (s, 3H, H-27), 1.34 (m, 1H, H-22′), 1.29 (m, 1H, H-21′), 1.28 (m, 1H, H-16′), 1.21 (s, 6H, H-25 and H-28), 1.15 (s, 3H, H-26), 1.09 (m, 1H, H-1′), 1.04 (m, 1H, H-15′), 0.98 (s, 3H, H-23), 0.94 (s, 3H, H-24), 0.87 (m, 1H, H-5), 0.79 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 200.0, 176.1, 169.0, 166.8, 144.3, 134.5, 133.8, 133.7, 130.2, 129.7, 129.7, 128.9, 128.9, 128.5, 128.0, 128.0, 127.0, 118.8, 80.7, 63.8, 61.7, 55.1, 53.5, 48.2, 45.4, 44.2, 43.2, 41.0, 38.9, 38.3, 37.7, 37.0, 32.7, 31.8, 31.2, 29.7, 28.4, 28.4, 28.1, 26.5, 26.4, 23.7, 23.3, 18.7, 17.4, 16.9, 16.5. HRMS (ES +) m/z calcd for $C_{46}H_{58}Cl_1O_5$ $[M + H]^+$: 725.3967, found 725.3979.

*4.2.2.19. 2-Bromobenzyl 3beta-cinnamoyloxy-11-oxo-olean-12-en-30-oate (**5c**)*. White solid, yield 32%, mp 185.7–187.4 °C. ^{1}H NMR ($CDCl_3$) δ: 7.67 (d, 1H, J = 16.0 Hz), 7.61 (dd, 1H, J = 8, 0.8 Hz), 7.55 (dt, 2H, J = 5.9, 3.7 Hz), 7.45 (dd, 1H, J = 7.6, 1.6 Hz), 7.36–7.40 (m, 2H), 7.31–7.41 (m, 2H), 7.22 (td, 1H, J = 7.7, 1.8 Hz), 6.46 (d, 1H, J = 16.0 Hz), 5.59 (s, 1H, H-12), 5.31 (s, 2H, Ph-C**H**$_2$), 4.68 (dd, 1H, H-3, J = 11.6, 4.8 Hz), 2.84 (dt, 1H, H-1, J = 13.5, 3.6 Hz), 2.38 (s, 1H, H-9), 2.08 (m, 1H, H-18), 2.04 (m, 1H, H-15), 1.97 (m, 1H, H-21), 1.96 (m, 1H, H-19), 1.82 (m, 1H, H-16), 1.76 (m, 1H, H-2), 1.72 (m, 1H, H-7), 1.69 (m, 1H, H-2′), 1.62 (m, 1H, H-19′), 1.55 (m, 1H, H-6), 1.49 (m, 1H, H-6′), 1.44 (m, 1H, H-7′), 1.42 (m, 1H, H-22), 1.37 (s, 3H, H-27), 1.34 (m, 1H, H-22′), 1.31 (m, 1H, H-21′), 1.27 (m, 1H, H-16′), 1.22 (s, 3H, H-25), 1.20 (s, 3H, H-28), 1.14 (s, 3H, H-26), 1.09 (m, 1H, H-1′), 1.04 (m, 1H, H-15′), 0.98 (s, 3H, H-23), 0.94 (s, 3H, H-24), 0.87 (m, 1H, H-5), 0.79 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 200.0, 176.0, 169.0, 166.8, 144.3, 135.4, 134.5, 132.9, 130.2, 130.2, 129.92, 128.9, 128.9, 128.53, 128.0, 128.0, 127.6, 123.6, 118.8, 80.7, 61.7, 55.0, 53.5, 48.2, 45.4, 44.1, 43.2, 41.0, 38.8, 38.3, 37.7, 37.0, 32.7, 31.8, 31.2, 28.5, 28.4, 28.1, 26.5, 26.4, 23.7, 23.3, 18.7, 17.4, 16.9, 16.5. HRMS (ES +) m/z calcd for $C_{46}H_{58}Br_1O_5$ $[M + H]^+$: 769.3462, found 769.3465.

*4.2.2.20. 2-Methylbenzyl 3beta-cinnamoyloxy-11-oxo-olean-12-en-30-oate (**5d**)*. White solid, yield 14%, mp 219.3–221.2 °C. ^{1}H NMR ($CDCl_3$) δ: 7.69 (d, 1H, J = 16.0 Hz), 7.51–7.60 (m, 2H), 7.33–7.46 (m, 4H), 7.19–7.32 (m, 3H), 6.47 (d, 1H, J = 16.0 Hz), 5.58 (s, 1H, H-12), 5.31 (s, 2H, Ph-C**H**$_2$), 4.68 (dd, 1H, H-3, J = 11.6, 4.8 Hz), 2.85 (dt, 1H, H-1, J = 13.4, 3.6 Hz), 2.39 (s, 4H), 2.08 (m, 1H, H-18), 2.03 (m, 1H, H-15), 1.97 (m, 1H, H-21), 1.95 (m, 1H, H-19), 1.83 (m, 1H, H-16), 1.78 (m, 1H, H-2), 1.73 (m, 1H, H-7), 1.69 (m, 1H, H-2′), 1.61 (m, 1H, H-19′), 1.58 (m, 1H, H-6), 1.47 (m, 1H, H-6′), 1.45 (m, 1H, H-7′), 1.41 (m, 1H, H-22), 1.38 (s, 3H, H-27), 1.35 (m, 1H, H-22′), 1.33 (m, 1H, H-21′), 1.28 (m, 1H, H-16′), 1.21 (s, 3H, H-25), 1.19 (s, 3H, H-28), 1.14 (s, 3H, H-26), 1.09 (m, 1H, H-1′), 1.04 (m, 1H, H-15′), 0.99 (s, 3H, H-23), 0.95 (s, 3H, H-24), 0.89 (m, 1H, H-5), 0.78 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 200.0, 176.2, 169.0, 166.8, 144.4, 136.7, 134.5, 134.0, 130.4, 130.2, 129.1, 128.9, 128.9, 128.5, 128.5, 128.1, 128.1, 126.1, 118.8, 80.7, 64.6, 61.7, 55.1 53.5, 48.3, 45.4, 44.1, 43.2, 41.1, 38.9, 38.3, 37.7, 37.0, 32.7, 31.8, 31.2, 28.5, 28.4, 28.1, 26.5, 26.4, 23.7, 23.3, 19.0, 18.7, 17.4, 16.9, 16.5. HRMS (ES +) m/z calcd for $C_{47}H_{61}O_5$ $[M + H]^+$: 705.4513, found 705.4525.

*4.2.2.21. 2-Fluorobenzyl 3beta-(4-methyl)cinnamoyloxy-11-oxo-olean-12-en-30-oate (**5e**)*. White solid, yield 3%, mp 164.2–166.5 °C. ^{1}H NMR ($CDCl_3$) δ: 7.66 (d, 1H, J = 16.0 Hz), 7.55 (dt, 3H, J = 5.9, 3.6 Hz), 7.30–7.46 (m, 5H), 7.07–7.22 (m, 2H), 6.42 (dd, 1H, J = 16.0, 1.2 Hz), 5.56 (s, 1H, H-12), 5.31 (s, 2H, Ph-C**H**$_2$), 4.68 (dd, 1H, H-3, J = 11.6, 4.8 Hz), 2.84 (d, 1H, H-1, J = 13.9 Hz), 2.39 (s, 3H), 2.36 (s, 1H, H-9), 2.08 (m, 1H, H-18), 2.04 (m, 1H, H-15), 1.97 (m, 1H, H-21), 1.94 (m, 1H, H-19), 1.82 (t, 1H, H-16, J = 14.1 Hz), 1.76 (m, 1H, H-2), 1.72 (m, 1H, H-7), 1.69 (m, 1H, H-2′), 1.61 (m, 1H, H-19′), 1.57 (m, 1H, H-6), 1.49 (m, 1H, H-6′), 1.44 (m, 1H, H-7′), 1.41 (m, 1H, H-22), 1.38 (s, 3H, H-27), 1.34 (m, 1H, H-22′), 1.31 (m, 1H, H-21′), 1.28 (m, 1H, H-16′), 1.25 (s, 3H, H-25), 1.19 (s, 3H, H-28), 1.15 (s, 3H, H-26), 1.11 (m, 1H, H-1′), 1.04 (m, 1H, H-15′), 0.98 (s, 3H, H-23), 0.94 (s, 3H, H-24), 0.88 (m, 1H, H-5), 0.77 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 200.0, 176.1, 169.0, 167.0, 159.8, 144.3, 140.5, 131.8, 130.4, 130.7, 129.6, 129.6, 128.5, 128.0, 128.0, 124.2, 124.2, 117.7, 115.7, 80.5, 61.7, 60.4, 55.1, 53.5, 48.2, 45.4, 44.1, 43.2, 41.0, 38.8, 38.3, 37.6, 36.9, 32.7, 31.8, 31.2, 29.7, 28.4, 28.3, 28.1, 26.5, 26.4, 23.7, 23.3, 21.5, 18.7, 17.4, 16.9, 16.5. HRMS (ES +) m/z calcd for $C_{47}H_{60}F_1O_5$ $[M + H]^+$: 723.4419, found 723.4435.

*4.2.2.22. 2-Chlorobenzyl 3beta-(4-methyl)cinnamoyloxy-11-oxo-olean-12-en-30-oate (**5f**)*. White solid, yield 14%, mp 209.5–212.1 °C. ^{1}H NMR ($CDCl_3$) δ: 7.66 (d, 1H, J = 16.0 Hz), 7.42–7.47 (m, 3H), 7.28–7.33 (m, 3H), 7.20 (d, 2H, J = 7.9 Hz), 6.46 (d, 1H, J = 16.0 Hz), 5.56 (s, 1H, H-12), 5.31 (s, 2H, Ph-C**H**$_2$), 4.68 (dd, 1H, H-3, J = 11.6, 4.9 Hz), 2.84 (dt, 1H, H-1, J = 13.5, 3.6 Hz), 2.39 (s, 3H), 2.10 (m, 1H, H-18), 2.06 (s, 1H, H-9), 2.00 (m, 1H, H-15), 1.99 (m, 1H, H-21), 1.96 (m, 1H, H-19), 1.84 (m, 1H, H-16), 1.75 (m, 1H, H-2), 1.72 (m, 1H, H-7), 1.69 (m, 1H, H-2′), 1.61 (m, 1H, H-19′), 1.53 (m, 1H, H-6), 1.50 (m, 1H, H-6′), 1.44 (m, 1H, H-7′), 1.42 (m, 1H, H-22), 1.38 (s, 3H, H-27), 1.34 (m, 1H, H-22′), 1.32 (m, 1H, H-21′), 1.27 (m, 1H, H-16′), 1.28 (s, 3H, H-25), 1.21 (s, 3H, H-28), 1.14 (s, 3H, H-26), 1.09 (m, 1H, H-1′), 1.04 (m, 1H, H-15′), 0.98 (s, 3H, H-23), 0.94 (s, 3H, H-24), 0.88 (m, 1H, H-5), 0.79 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 200.0, 176.1, 169.0, 167.01, 144.4, 140.5, 133.8, 133.7, 130.2, 129.7, 129.7, 129.6, 129.6, 128.7, 128.5, 128.0, 128.0, 127.0, 117.7, 80.5, 63.9, 61.7, 55.1, 53.5, 48.2, 45.4, 44.2, 43.2, 41.0, 38.9, 38.3, 37.7, 37.0, 32.7, 31.8, 31.2, 29.7, 28.4, 28.4, 28.1, 26.5, 26.4, 23.7, 23.3, 21.5, 18.7, 17.4, 16.9, 16.5. HRMS (ES +) m/z calcd for $C_{47}H_{60}Cl_1O_5$ $[M + H]^+$: 739.4124, found 739.4131.

*4.2.2.23. 2-Bromobenzyl 3beta-(4-methyl)cinnamoyloxy-11-oxo-olean-12-en-30-oate (**5g**)*. White solid, yield 2%, mp 196.8–198.9 °C. ^{1}H NMR ($CDCl_3$) δ: 7.55–7.68 (m, 2H), 7.40–7.46 (m, 3H), 7.35–7.39 (m, 2H), 7.22 (dt, J = 8.1, 4.0 Hz, 2H), 6.42 (d , 1H, J = 2.0 Hz), 5.59 (s, 1H, H-12), 5.32 (s, 2H, Ph-C**H**$_2$), 4.67 (m, 1H, H-3), 2.84 (d, 1H, H-1, J = 13.6 Hz), 2.39 (s, 3H), 2.36 (s, 1H, H-9), 2.06 (m, 1H, H-18), 2.02 (m, 1H, H-15), 1.98 (m, 1H, H-21), 1.90 (m, 1H, H-19), 1.84 (m, 1H, H-16), 1.75 (m, 1H, H-2), 1.73 (m, 1H, H-7), 1.69 (m, 1H, H-2′), 1.61 (m, 1H, H-19′), 1.53 (m, 1H, H-6), 1.49 (m, 1H, H-6′), 1.45 (m, 1H, H-7′), 1.41 (m, 1H, H-22), 1.39 (s, 3H, H-27), 1.34 (m, 1H, H-22′), 1.31 (m, 1H, H-21′), 1.28 (m, 1H, H-16′), 1.22 (s, 3H, H-25), 1.19 (s, 3H, H-28), 1.15 (s, 3H, H-26), 1.09 (m, 1H, H-1′), 1.04 (m, 1H, H-15′), 0.98 (s, 3H, H-23), 0.94 (s, 3H, H-24), 0.88 (m, 1H, H-5), 0.79 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 200.0, 176.0, 169.0, 167.0, 144.3, 140.5, 135.4, 133.0, 133.0, 132.8, 130.2, 129.9, 129.7, 129.6, 128.5, 128.0, 127.6, 127.5, 123.7, 117.7, 85.6, 66.0, 61.7, 55.1, 53.4, 48.2, 45.4, 45.4, 44.2, 43.2, 41.0, 38.9, 38.3, 37.7, 36.9, 32.7, 31.8, 31.2, 28.4, 28.4, 28.1, 26.5, 26.4, 23.7, 23.3, 21.5, 18.7, 17.4, 16.9, 16.6. HRMS (ES +) m/z calcd for $C_{47}H_{60}Br_1O_5$ $[M + H]^+$: 783.3619, found 783.3636.

*4.2.2.24. 2-Methylbenzyl 3beta-(4-methyl)cinnamoyloxy-11-oxo-olean-12-en-30-oate (**5h**)*. White solid, yield 7%, mp 167.8–169.2 °C. ^{1}H NMR ($CDCl_3$) δ: 7.66 (d, 1H, J = 16.0 Hz), 7.45 (d, 2H, J = 8.0 Hz), 7.36 (dd, 1H, J = 7.4, 1.8 Hz), 7.32–7.17 (m, 5H), 6.42 (d, 1H, J = 16.0 Hz), 5.57 (s, 1H, H-12), 5.32 (s, 2H, Ph-C**H**$_2$), 4.68 (dd, 1H, H-3, J = 11.6, 4.8 Hz), 2.85 (dt, 1H, H-1, J = 13.4, 3.6 Hz), 2.39 (s, 6H), 2.37 (s, 1H, H-9), 2.07 (m, 1H, H-18), 2.05 (m, 1H, H-15), 1.97 (m, 1H, H-21), 1.95 (m, 1H, H-19), 1.83 (m, 1H, H-16), 1.77 (m, 1H, H-2), 1.72 (m, 1H, H-7), 1.69 (m, 1H, H-2′), 1.61 (m, 1H, H-19′), 1.54 (m, 1H, H-6), 1.49 (m, 1H, H-6′), 1.44 (m, 1H, H-7′), 1.41 (m, 1H, H-22), 1.38 (s, 3H, H-27), 1.36 (m, 1H, H-22′), 1.33 (m, 1H, H-21′), 1.26 (m, 1H, H-16′), 1.21 (s, 3H, H-25), 1.19 (s, 3H, H-28), 1.14 (s, 3H, H-26), 1.10 (m,

1H, H-1′), 1.04 (m, 1H, H-15′), 0.98 (s, 3H, H-23), 0.94 (s, 3H, H-24), 0.89 (m, 1H, H-5), 0.78 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 200.0, 176.2, 169.0, 167.0, 144.4, 140.5, 136.7, 134.0, 131.8, 130.4, 129.6, 129.6, 129.1, 128.5, 128.5, 128.0, 128.0, 126.1, 117.7, 80.5, 64.6, 61.7, 55.1, 53.5, 48.3, 45.4, 44.1, 43.2, 41.1, 38.9, 38.3, 37.7, 37.0, 32.7, 31.8, 31.2, 28.5, 28.4, 28.1, 26.5, 26.4, 23.7, 23.3, 21.5, 19.0, 18.7, 17.4, 16.9, 16.5. HRMS (ES +) *m/z* calcd for $C_{48}H_{63}O_5$ $[M + H]^+$: 719.4670, found 719.4680.

4.2.2.25. 2-Fluorobenzyl 3beta-(4-fluoro)cinnamoyloxy-11-oxo-olean-12-en-30-oate ***(5i)***. White solid, yield 21%, mp 193.3–195.1 °C. ^{1}H NMR ($CDCl_3$) δ: 7.63 (d, 1H, *J* = 16.0 Hz), 7.52 (dd, 2H, *J* = 8.5, 5.4 Hz), 7.26–7.44 (m, 2H), 7.03–7.23 (m, 4H), 6.37 (d, 1H, *J* = 16.0 Hz), 5.55 (s, 1H, H-12), 5.30 (s, 2H, Ph-C**H**$_2$), 4.68 (dd, 1H, H-3, *J* = 11.7, 4.8 Hz), 2.83 (dt, 1H, H-1, *J* = 13.5, 3.6 Hz), 2.37 (s, 1H, H-9), 2.07 (m, 1H, H-18), 2.04 (m, 1H, H-15), 1.95 (m, 1H, H-21), 1.92 (m, 1H, H-19), 1.84 (m, 1H, H-16), 1.78 (m, 1H, H-2), 1.74 (m, 1H, H-7), 1.68 (m, 1H, H-2′), 1.63 (m, 1H, H-19′), 1.59 (m, 1H, H-6), 1.48 (m, 1H, H-6′), 1.43 (m, 1H, H-7′), 1.39 (m, 1H, H-22), 1.36 (s, 3H, H-27), 1.33 (m, 1H, H-22′), 1.30 (m, 1H, H-21′), 1.26 (m, 1H, H-16′), 1.19 (s, 3H, H-25), 1.17 (s, 3H, H-28), 1.13 (s, 3H, H-26), 1.07 (m, 1H, H-1′), 1.02 (m, 1H, H-15′), 0.97 (s, 3H, H-23), 0.93 (s, 3H, H-24), 0.87 (m, 1H, H-5), 0.76 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 200.0, 176.1, 169.0, 166.6, 162.3, 159.8, 143.0, 130.8, 130.7, 130.4, 130.4, 129.9, 129.9, 128.4, 124.2, 116.1, 115.9, 115.7, 115.5, 80.7, 61.7, 60.4, 60.3, 55.0, 53.5, 48.2, 45.4, 44.0, 43.2, 41.0, 38.8, 38.3, 37.6, 36.9, 32.7, 31.2, 28.4, 28.3, 28.1, 26.5, 23.7, 23.3, 18.7, 17.4, 16.9, 16.4. HRMS (ES +) *m/z* calcd for $C_{46}H_{57}F_2O_5$ $[M + H]^+$: 727.4168, found 727.4182.

4.2.2.26. 2-Chlorobenzyl 3beta-(4-fluoro)cinnamoyloxy-11-oxo-olean-12-en-30-oate ***(5j)***. White solid, yield 13%, mp 118.2–119.7 °C. ^{1}H NMR ($CDCl_3$) δ: 7.64 (d, 1H, *J* = 16.0 Hz), 7.49–7.57 (m, 2H), 7.41 –7.46(m, 2H), 7.31 (dt, *J* = 7.0, 2.2 Hz, 2H), 7.03–7.13 (m, 2H), 6.37 (d, 1H, *J* = 16.0 Hz), 5.57 (s, 1H, H-12), 5.31 (s, 2H, Ph-C**H**$_2$), 4.67 (dd, 1H, H-3, *J* = 11.7, 4.8 Hz), 2.84 (dt, 1H, H-1, *J* = 13.6, 3.7 Hz), 2.38 (s, 1H, H-9), 2.09 (m, 1H, H-18), 2.00 (m, 1H, H-15), 1.99 (m, 1H, H-21), 1.95 (m, 1H, H-19), 1.86 (m, 1H, H-16), 1.78 (m, 1H, H-2), 1.73 (m, 1H, H-7), 1.68 (m, 1H, H-2′), 1.65 (m, 1H, H-19′), 1.60 (m, 1H, H-6), 1.49 (m, 1H, H-6′), 1.43 (m, 1H, H-7′), 1.39 (m, 1H, H-22), 1.38 (s, 3H, H-27), 1.33 (m, 1H, H-22′), 1.29 (m, 1H, H-21′), 1.27 (m, 1H, H-16′), 1.21 (s, 3H, H-25), 1.20 (s, 3H, H-28), 1.13 (s, 3H, H-26), 1.08 (m, 1H, H-1′), 1.04 (m, 1H, H-15′), 0.97 (s, 3H, H-23), 0.93 (s, 3H, H-24), 0.84 (m, 1H, H-5), 0.78 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 200.0, 176.0, 166.7, 162.6, 143.0, 133.7, 133.6, 130.2, 130.2, 129.9, 129.9, 129.7, 129.7, 129.7, 128.5, 127.0, 118.6, 116.1, 115.9, 80.7, 63.8, 61.7, 55.0, 48.2, 45.4, 44.2, 43.2, 41.0, 38.8, 38.3, 37.6, 36.9, 32.7, 31.8, 31.2, 28.4, 28.4, 28.1, 26.5, 26.40 , 23.7, 23.3, 18.7, 17.4, 16.9, 16.5. HRMS (ES +) *m/z* calcd for $C_{46}H_{57}Cl_1F_1O_5$ $[M + H]^+$: 743.3873, found 743.3882.

4.2.2.27. 2-Bromobenzyl 3beta-(4-fluoro)cinnamoyloxy-11-oxo-olean-12-en-30-oate ***(5k)***. White solid, yield 2%, mp 115.6–117.8 °C. ^{1}H NMR ($CDCl_3$) δ: 7.59–7.68 (m, 2H), 7.51–7.54 (m, 2H), 7.45 (dd, 1H, *J* = 7.6, 1.8 Hz), 7.36 (td, 1H, *J* = 7.5, 1.2 Hz), 7.22 (td, *J* = 7.7, 1.8 Hz, 1H), 7.08 (t, 2H, *J* = 8.6 Hz), 6.38 (d, 1H, *J* = 16.0 Hz), 5.59 (s, 1H, H-12), 5.31 (s, 2H, Ph-C**H**$_2$), 4.67 (dd, 1H, H-3, *J* = 11.6, 4.8 Hz), 2.85 (m, 1H, H-1), 2.38 (s, 1H, H-9), 2.07 (m, 1H, H-18), 2.04 (m, 1H, H-15), 1.97 (m, 1H, H-21), 1.96 (m, 1H, H-19), 1.82 (m, 1H, H-16), 1.78 (m, 1H, H-2), 1.74 (m, 1H, H-7), 1.68 (m, 1H, H-2′), 1.62 (m, 1H, H-19′), 1.60 (m, 1H, H-6), 1.49 (m, 1H, H-6′), 1.44 (m, 1H, H-7′), 1.40 (m, 1H, H-22), 1.38 (s, 3H, H-27), 1.37 (m, 1H, H-22′), 1.34 (m, 1H, H-21′), 1.27 (m, 1H, H-16′), 1.22 (s, 3H, H-25), 1.20 (s, 3H, H-28), 1.13 (s, 3H, H-26), 1.08 (m, 1H, H-1′), 1.04 (m, 1H, H-15′), 0.97 (s, 3H, H-23), 0.93 (s, 3H, H-24), 0.82 (m, 1H, H-5), 0.79 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 200.0, 176.0, 169.1, 166.7, 162.6, 143.0, 132.9, 132.9, 130.2, 129.9, 129.9, 129.9, 129.9, 128.5, 127.6, 123.6, 118.5, 116.1, 115.9, 80.7, 66.0, 61.7, 55.0, 53.5, 48.2, 45.4, 44.2, 43.2, 41.0, 38.8, 38.3, 37.7, 36.9, 32.7, 31.8, 31.2, 28.5, 28.4, 28.1, 26.5, 26.4, 23.7, 23.3, 18.7, 17.4, 16.9, 16.5. HRMS (ES +) *m/z* calcd for $C_{46}H_{57}Br_1F_1O_5$ $[M + H]^+$: 787.3368, found 787.3368.

4.2.2.28. 2-Methylbenzyl 3beta-(4-fluoro)cinnamoyloxy-11-oxo-olean-12-en-30-oate ***(5l)***. White solid, yield 2%, mp 101.2–102.9 °C. ^{1}H NMR ($CDCl_3$) δ: 7.65 (d, 1H, *J* = 15.9 Hz), 7.54 (t, 2H, *J* = 6.9 Hz), 7.36 (d, 1H, *J* = 7.1 Hz), 7.25 (dt, 3H, *J* = 15.1, 6.4 Hz), 7.09 (t, 2H, *J* = 8.5 Hz), 6.37 (d, 1H, *J* = 15.6 Hz), 5.57 (s, 1H, H-12), 5.32 (s, 2H, Ph-C**H**$_2$), 4.68 (dd, 1H, H-3, *J* = 11.6, 4.0 Hz), 2.85 (d, 1H, H-1, *J* = 13.6 Hz), 2.39 (s, 3H), 2.35 (s, 1H, H-9), 2.09 (m, 1H, H-18), 2.03 (m, 1H, H-15), 1.95 (m, 1H, H-21), 1.92 (m, 1H, H-19), 1.86 (m, 1H, H-16), 1.79 (m, 1H, H-2), 1.73 (m, 1H, H-7), 1.67 (m, 1H, H-2′), 1.65 (m, 1H, H-19′), 1.58 (m, 1H, H-6), 1.47 (m, 1H, H-6′), 1.45 (m, 1H, H-7′), 1.41 (m, 1H, H-22), 1.38 (s, 3H, H-27), 1.33 (m, 1H, H-22′), 1.30 (m, 1H, H-21′), 1.26 (m, 1H, H-16′), 1.21 (s, 3H, H-25), 1.19 (s, 3H, H-28), 1.14 (s, 3H, H-26), 1.07 (m, 1H, H-1′), 1.02 (m, 1H, H-15′), 0.98 (s, 3H, H-23), 0.94 (s, 3H, H-24), 0.85 (m, 1H, H-5), 0.77 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 200.0, 176.2, 169.0, 166.7, 162.6, 143.0, 136.7, 134.0, 130.8, 130.4, 129.9, 129.9, 129.1, 128.5, 128.5, 126.1, 118.6, 116.1, 115.9, 80.7, 64.6, 61.7, 55.1, 48.3, 45.4, 44.1, 43.2, 41.1, 38.8, 38.3, 37.7, 37.0, 32.7, 31.2, 28.5, 28.4, 28.1, 26.4, 23.7, 23.3, 19.0, 18.7, 17.4, 16.9, 16.4. HRMS (ES +) *m/z* calcd for $C_{47}H_{60}F_1O_5$ $[M + H]^+$: 723.4419, found 723.4435.

4.2.2.29. 2-Fluorobenzyl 3beta-(4-nitro)cinnamoyloxy-11-oxo-olean-12-en-30-oate ***(5m)***. White solid, yield 26%, mp 106.8–108.5 °C. ^{1}H NMR ($CDCl_3$) δ: 8.12–8.24 (m, 2H), 7.62–7.71 (m, 3H), 7.25–7.41 (m, 2H), 7.04–7.15 (m, 2H), 6.55 (d, 1H, *J* = 20.0 Hz), 5.51 (s, 1H, H-12), 5.27 (s, 2H, Ph-C**H**$_2$), 4.65 (dd, 1H, H-3, *J* = 12.0, 4.8 Hz), 2.80 (m, 1H, H-1), 2.34 (s, 1H, H-9), 2.04 (m, 1H, H-18), 2.00 (m, 1H, H-15), 1.95 (m, 1H, H-21), 1.91 (m, 1H, H-19), 1.88 (m, 1H, H-16), 1.78 (m, 1H, H-2), 1.75 (m, 1H, H-7), 1.67 (m, 1H, H-2′), 1.64 (m, 1H, H-19′), 1.59 (m, 1H, H-6), 1.48 (m, 1H, H-6′), 1.42 (m, 1H, H-7′), 1.40 (m, 1H, H-22), 1.33 (s, 3H, H-27), 1.29 (m, 1H, H-22′), 1.27 (m, 1H, H-21′), 1.22 (m, 1H, H-16′), 1.16 (s, 3H, H-25), 1.14 (s, 3H, H-28), 1.09 (s, 3H, H-26), 1.03 (m, 1H, H-1′), 0.99 (m, 1H, H-15′), 0.94 (s, 3H, H-23), 0.90 (s, 3H, H-24), 0.84 (m, 1H, H-5), 0.72 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 199.8, 176.0, 169.1, 165.8, 159.7, 148.4, 141.3, 140.7, 130.7, 130.2, 128.6, 128.6, 128.4, 124.2, 124.1, 124.1, 123.1, 115.6, 115.4, 81.4, 61.6, 60.3, 55.0, 53.5, 48.2, 45.3, 44.0, 43.1, 41.0, 38.7, 38.2, 37.6, 36.9, 32.6, 31.7, 31.1, 28.4, 28.2, 28.1, 26.4, 23.6, 23.3, 18.6, 17.4, 16.9, 16.4. HRMS (ES +) *m/z* calcd for $C_{46}H_{57}F_1N_1O_7$ $[M + H]^+$: 754.4113, found 754.4121.

4.2.2.30. 2-Chlorobenzyl 3beta-(4-nitro)cinnamoyloxy-11-oxo-olean-12-en-30-oate ***(5n)***. White solid, yield 41%, mp 143.1–144.5 °C. ^{1}H NMR ($CDCl_3$) δ: 8.13–8.25 (m, 2H), 7.62–7.72 (m, 3H), 7.35–7.45 (m, 2H), 7.24–7.31 (m, 2H), 6.56 (dd, 1H, *J* = 16.1, 2.7 Hz), 5.54 (s, 1H, H-12), 5.28 (s, 2H, Ph-C**H**$_2$), 4.66 (dd, 1H, H-3, *J* = 11.3, 4.6 Hz), 2.81 (m, 1H, H-1), 2.35 (s, 1H, H-9), 2.07 (m, 1H, H-18), 2.01 (m, 1H, H-15), 1.96 (m, 1H, H-21), 1.92 (m, 1H, H-19), 1.87 (m, 1H, H-16), 1.79 (m, 1H, H-2), 1.76 (m, 1H, H-7), 1.66 (m, 1H, H-2′), 1.63 (m, 1H, H-19′), 1.58 (m, 1H, H-6), 1.49 (m, 1H, H-6′), 1.46 (m, 1H, H-7′), 1.41 (m, 1H, H-22), 1.35 (s, 3H, H-27), 1.33 (m, 1H, H-22′), 1.30 (m, 1H, H-21′), 1.23 (m, 1H, H-16′), 1.17 (s, 3H, H-25), 1.11 (s, 3H, H-28), 1.08 (s, 3H, H-26), 1.05 (m, 1H, H-1′), 1.01 (m, 1H, H-15′), 0.95 (s, 3H, H-23), 0.91 (s, 3H, H-24), 0.84 (m, 1H, H-5), 0.75 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 199.9, 176.0, 169.1, 148.4, 141.4, 140.7, 133.7, 133.7, 130.2, 130.1, 129.7, 129.6, 128.6, 128.4, 127.0, 124.1, 123.8, 123.1, 123.1, 81.3, 63.7, 61.6, 55.0, 53.5, 48.2, 45.3, 44.1, 43.2, 41.0, 38.8, 38.3, 37.7, 36.9, 32.6, 31.8, 31.2, 28.4, 28.1, 28.0, 26.4, 26.4, 23.6, 23.3, 18.7, 17.4, 16.9, 16.4. HRMS (ES +) *m/z* calcd for $C_{46}H_{57}Cl_1N_1O_7$ $[M + H]^+$: 770.3818, found 770.3833.

*4.2.2.31. 2-Bromobenzyl 3beta-(4-nitro)cinnamoyloxy-11-oxo-olean-12-en-30-oate (**5o**)*. White solid, yield 49%, mp 132.4–134.8 °C. ^{1}H NMR ($CDCl_3$) δ: 8.13–8.25 (m, 2H), 7.62–7.72 (m, 3H), 7.56 (dt, 1H, *J* = 7.9, 1.5 Hz), 7.26–7.45 (m, 2H), 7.18 (tt, 1H, *J* = 7.6, 1.7 Hz), 6.56 (d, 1H, *J* = 16.0 Hz), 5.56 (s, 1H, H-12), 5.28 (s, 2H, Ph-C**H**$_2$), 4.66 (dd, 1H, H-3, *J* = 11.6, 4.8 Hz), 2.80 (ddt, 1H, *J* = 16.7, 13.8, 3.5 Hz), 2.35 (s, 1H, H-9), 2.10 (m, 1H, H-18), 2.02 (m, 1H, H-15), 1.96 (m, 1H, H-21), 1.92 (m, 1H, H-19), 1.85 (m, 1H, H-16), 1.78 (m, 1H, H-2), 1.75 (m, 1H, H-7), 1.67 (m, 1H, H-2′), 1.64 (m, 1H, H-19′), 1.59 (m, 1H, H-6), 1.48 (m, 1H, H-6′), 1.42 (m, 1H, H-7′), 1.40 (m, 1H, H-22), 1.35 (s, 3H, H-27), 1.29 (m, 1H, H-22′), 1.27 (m, 1H, H-21′), 1.22 (m, 1H, H-16′), 1.19 (s, 3H, H-25), 1.16 (s, 3H, H-28), 1.10 (s, 3H, H-26), 1.03 (m, 1H, H-1′), 0.99 (m, 1H, H-15′), 0.95 (s, 3H, H-23), 0.91 (s, 3H, H-24), 0.85 (m, 1H, H-5), 0.76 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 199.8, 175.9, 169.1, 165.8, 148.4, 141.3, 140.7, 135.3, 132.9, 130.2, 130.1, 129.9, 128.6, 128.4, 127.6, 124.1, 123.6, 123.1, 123.1, 81.3, 65.9, 61.6, 55.0, 53.5, 48.2, 45.3, 44.1, 43.2, 41.0, 38.8, 38.2, 37.7, 36.9, 32.6, 31.8, 31.1, 28.4, 28.1, 28.0, 26.4, 23.6, 23.3, 18.7, 17.4, 16.9, 16.4. HRMS (ES +) *m/z* calcd for $C_{46}H_{57}Br_1N_1O_7$ $[M + H]^+$: 814.3313, found 814.3306.

*4.2.2.32. 2-Methylbenzyl 3beta-(4-nitro)cinnamoyloxy-11-oxo-olean-12-en-30-oate (**5p**)*. White solid, yield 44%, mp 111.6–113.2 °C. ^{1}H NMR ($CDCl_3$) δ: 8.13–8.25 (m, 2H), 7.63–7.72 (m, 3H), 7.22 (m, 1H), 7.15–7.28 (m, 3H), 6.57 (d, 1H, *J* = 16.0 Hz), 5.55 (s, 1H, H-12), 5.27 (s, 2H, Ph-C**H**$_2$), 4.68 (dd, 1H, H-3, *J* = 11.6, 4.8 Hz), 2.82 (ddt, 1H, H-1, *J* = 16.9, 13.9, 3.6 Hz), 2.36 (s, 3H), 2.31 (s, 1H, H-9), 2.04 (m, 1H, H-18), 2.02 (m, 1H, H-15), 1.96 (m, 1H, H-21), 1.92 (m, 1H, H-19), 1.84 (m, 1H, H-16), 1.77 (m, 1H, H-2), 1.74 (m, 1H, H-7), 1.67 (m, 1H, H-2′), 1.64 (m, 1H, H-19′), 1.58 (m, 1H, H-6), 1.48 (m, 1H, H-6′), 1.42 (m, 1H, H-7′), 1.39 (m, 1H, H-22), 1.36 (s, 3H, H-27), 1.31 (m, 1H, H-22′), 1.28 (m, 1H, H-21′), 1.25 (m, 1H, H-16′), 1.18 (s, 3H, H-25), 1.16 (s, 3H, H-28), 1.11 (s, 3H, H-26), 1.06 (m, 1H, H-1′), 1.01 (m, 1H, H-15′), 0.96 (s, 3H, H-23), 0.92 (s, 3H, H-24), 0.86 (m, 1H, H-5), 0.72 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 199.83 , 176.13 , 169.12 , 165.77 , 148.4, 141.4, 140.7, 136.6, 134.0, 130.4, 130.3, 129.1, 128.7, 128.5, 128.4, 126.1, 124.1, 123.1, 123.1, 81.4, 64.5, 61.6, 55.0, 53.5, 48.2, 45.3, 44.1, 43.2, 41.1, 38.8, 37.7, 36.9, 32.7, 31.8, 31.1, 28.5, 28.1, 28.1, 26.4, 23.6, 23.3, 19.0, 18.6, 17.4, 16.9, 16.4. HRMS (ES +) *m/z* calcd for $C_{47}H_{60}N_1O_7$ $[M + H]^+$: 750.4364, found 750.4362.

*4.2.2.33. 2-Fluorobenzyl 3beta-(2,3,4,5,6-Pentafluoro)cinnamoyloxy-11-oxo-olean-12-en-30-oate (**5q**)*. White solid, yield 26%, mp 198.7–199.5 °C. ^{1}H NMR ($CDCl_3$) δ: 7.62 (d, 1H, *J* = 16.4 Hz), 7.26–7.43 (m, 2H), 7.12 (dt, 2H, *J* = 26.5, 8.4 Hz), 6.74 (d, 1H, *J* = 20.0 Hz), 5.54 (s, 2H, Ph-C**H**$_2$), 5.26 (d, 1H, H-12, *J* = 12.4 Hz), 4.67 (dd, 1H, H-3, *J* = 12.0, 4.8 Hz), 2.80 (d, 1H, H-1, *J* = 13.6 Hz), 2.36 (s, 1H, H-9), 2.06 (m, 1H, H-18), 2.01 (m, 1H, H-15), 1.95 (m, 1H, H-21), 1.91 (m, 1H, H-19), 1.84 (m, 1H, H-16), 1.78 (m, 1H, H-2), 1.71 (m, 1H, H-7), 1.68 (m, 1H, H-2′), 1.62 (m, 1H, H-19′), 1.59 (m, 1H, H-6), 1.48 (m, 1H, H-6′), 1.42 (m, 1H, H-7′), 1.40 (m, 1H, H-22), 1.36 (s, 3H, H-27), 1.30 (m, 1H, H-22′), 1.26 (m, 1H, H-21′), 1.25 (m, 1H, H-16′), 1.18 (s, 3H, H-25), 1.17 (s, 3H, H-28), 1.12 (s, 3H, H-26), 1.02 (m, 1H, H-1′), 0.98 (m, 1H, H-15′), 0.95 (s, 3H, H-23), 0.92 (s, 3H, H-24), 0.86 (m, 1H, H-5), 0.75 (s, 3H, H-29); ^{13}C NMR ($CDCl_3$) δ: 199.8, 176.0, 169.0, 165.7, 159.8, 148.0, 144.3, 138.9, 136.5, 130.7, 130.4, 130.3, 128.4, 127.8, 126.9, 124.2, 124.1, 115.6, 115.4, 81.6, 61.6, 60.3, 55.0, 48.2, 45.3, 44.0, 43.2, 41.0, 38.8, 38.2, 37.6, 36.9, 32.7, 31.7, 31.1, 28.4, 28.2, 28.1, 26.4, 23.6, 23.3, 18.7, 17.4, 16.8, 16.4. HRMS (ES +) *m/z* calcd for $C_{46}H_{53}F_6O_5$ $[M + H]^+$: 799.3791, found 799.3798.

4.3. Biological assays

4.3.1. Cytotoxicity in vitro assay

MTT assay was used to determine the cytotoxicity *in vitro*. The MCF-7, HeLa cell lines and L-O2 (3–4 × 10^4 cells/mL) were placed in 96-well plates and cultured in an incubator at 37 °C with 5% CO_2 for 24 h. Then, the medium was replaced by various concentrations of test compounds. After 48 h incubation, 20 μL of MTT solution (5 mg/mL) was added to each well and it was incubated for another 4 h. The formazan crystals were dissolved in 100 μL DMSO and the absorbance was measured at 490 nm using a Bio-Rad iMark™ microplate reader. The IC_{50} values were obtained by linear regression analysis using GraphPad Prism (version 5.01).

4.3.2. Apoptosis assay by Hoechst 33,342 staining methods

HeLa cells were seeded into 6-well plates and incubated at 37 °C with 5% CO_2 for 24 h. Then, the medium was replaced by different concentrations of compounds **2d** (0 μM, 2 μM, 4 μM) and **3o** (0 μM, 1 μM, 2 μM) for 48 h. After that, the cells were fixed with 4% paraformaldehyde and stained with DMEM solution containing 10 μg/mL Hoechst 33,342 for 10 min in the dark. Finally, the cells were washed twice with cold PBS and examined under a fluorescence microscope.

4.3.3. Apoptosis assay by AO/EB staining methods

HeLa cells were seeded into 6-well plates and incubated at 37 °C with 5% CO_2 for 24 h. Then, the cells were exposed to different concentrations of compounds **2d** (0 μM, 2 μM, 4 μM) and **3o** (0 μM, 1 μM, 2 μM) for 48 h. After that, the cells were trypsinized, fixed and stained with 100 μg/mL concentration of AO/EB for 5 min in the dark. Finally, the cells were washed twice with cold PBS and examined under a fluorescence microscope.

4.3.4. Reactive oxygen species (ROS) assay

Intracellular ROS levels were measured using 2′, 7′-dichlorodihydrofluorescein diacetate (DCFH-DA) fluorescent probe. After incubation with different concentrations of compounds **2d** and **3o**, the cells were trypsinized and incubated with 10 μM DCFH-DA in DMEM for 25 min in the dark. Finally, the cells were washed twice with cold PBS and examined under a fluorescence microscope.

4.3.5. Apoptosis assay by annexin V/7-AAD double staining

PE Annexin V Apoptosis Detection Kit I was used to distinguish different stages of apoptosis. After incubation with different concentrations of compounds **2d** and **3o** for 48 h, the cells were trypsinized and washed twice with PBS. Then, the cells were stained with Annexin V-PE (5 μL) and 7-AAD (5 μL) in binding buffer. After incubation at room temperature for 15 min, cell apoptosis was analyzed by BD FACS Aria III flow cytometer.

4.3.6. Autophagy induced by the compounds

HeLa cells were seeded into 6-well plates and incubated for 24 h. Then, the medium was replaced with medium containing different concentrations of compounds **2d** (0 μM, 2 μM, 4 μM) and **3o** (0 μM, 1 μM, 2 μM) for 48 h. After that, the cells were trypsinized and stained with MDC (monodansylcadaverine) solution (50 mM) for 15 min in the dark. Finally, the cells were washed twice with cold PBS and analyzed by BD FACS Aria III flow cytometer.

Acknowledgements

The authors are grateful for the Fundamental Research Funds for the Innovation and Entrepreneurship Foundation from Huancui District of Wehai City, the project of Weihai Science and Technology Bureau (No. 1070432121708), the National Natural Science Foundation of China (21672046 and 21372054) and the Fundamental Research Funds for the Central Universities (HIT.NSRIF.201701). Mass spectrometry was made possible by the support of the Hercules Foundation of the Flemish Government (grant 20100225–7). R.W. acknowledges the Peterson "Serving Hometown" Elites Scholarship for providing a doctoral funding.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2108: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (2018) (2018) 394–424, https://doi.org/10.3322/caac.21492.

[2] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2018, CA Cancer J. Clin. 60 (2018) 277–300, https://doi.org/10.3322/caac.21442.

[3] H. Yuan, Q. Ma, L. Ye, G. Piao, The traditional medicine and modern medicine from natural products, Molecules 21 (2016) 559, https://doi.org/10.3390/molecules21050559.

[4] A. Stierle, Review of cancer inhibitors from Chinese natural medicines, J. Nat. Prod. 81 (2018) 1125–1126, https://doi.org/10.1021/acs.jnatprod.8b00014.

[5] S. Safe, R. Kasiappan, Natural products as mechanism-based anticancer agents: Sp transcription factors as targets, Phytother. Res. 30 (2016) 1723–1732, https://doi.org/10.1002/ptr.5669.

[6] F. Mengoni, M. Lichtner, L. Battinelli, M. Marzi, C.M. Mastroianni, V. Vullo, G. Mazzanti, In vitro anti-HIV activity of oleanolic acid on infected human mononuclear cells, Planta Med. 68 (2002) 111–114, https://doi.org/10.1055/s-2002-20256.

[7] L.B. Kong, S.S. Li, Q.J. Liao, Y.N. Zhang, R.N. Sun, X.D. Zhu, Q.H. Zhang, J. Wang, X.Y. Wu, X.N. Fang, Y. Zhu, Oleanolic acid and ursolic acid: novel hepatitis C virus antivirals that inhibit NS5B activity, Antivir. Res. 98 (2013) 44–53, https://doi.org/10.1016/j.antiviral.2013.02.003.

[8] M. Antonela Zígolo, M. Salinas, L. Alché, A. Baldessari, L. Guadalupe García, Chemoenzymatic synthesis of new derivatives of glycyrrhetinic acid with antiviral activity. Molecular docking study, Bioorg. Chem. 78 (2018) 210, https://doi.org/10.1016/j.bioorg.2018.03.018 219.

[9] M.E. Hardy, J.M. Hendricks, J.M. Paulson, N.R. Faunce, 18 β-glycyrrhetinic acid inhibits rotavirus replication in culture, Virol. J. 9 (2012) 96, https://doi.org/10.1186/1743-422X-9-96.

[10] G.J. Kim, H.J. Jo, K.H. Chung, K.J. Lee, J.H. An, Oleanolic acid induces p53 dependent apoptosis via the erk/jnk/akt pathway in cancer cell lines, Oncotarget 9 (2018) 26370–26386, https://doi.org/10.18632/oncotarget.25316.

[11] L. Žiberna, D. Šamec, A. Mocan, S.F. Nabavi, A. Bishayee, A.A. Farooqi, A. Sureda, S.M. Nabavi, Oleanolic acid alters multiple cell signaling pathways: implication in cancer prevention and therapy, Int. J. Mol. Sci. 18 (2017) 643, https://doi.org/10.3390/ijms18030643.

[12] Y.Y. Zhu, H.Y. Huang, Y.L. Wu, Anticancer and apoptotic activities of oleanolic acid are mediated through cell cycle arrest and disruption of mitochondrial membrane potential in HepG2 human hepatocellular carcinoma cells, Mole. Med. Rep. 12 (2015) 5012–5018, https://doi.org/10.3892/mmr.2015.4033.

[13] Z.B. Gao, X. Kang, C.L. Xu, Research progress of anticancer mechanism of glycyrrhetinic acid, China, J. Chinese Mater. Med. 36 (2011) 3213–3216, https://doi.org/10.1007/s10570-010-9464-0.

[14] H. Singh, S.J. Kim, D.H. Kang, H.R. Kim, A. Sharma, W.Y. Kim, C.H. Kang, J.S. Kim, Glycyrrhetinic acid as a hepatocyte targeting unit for an anticancer drug delivery system with enhanced cell type selectivity, Chem. Commun. 54 (2018) 12353–12356, https://doi.org/10.1039/C8CC05175E.

[15] Y.M. Lu, M.Y. Zhu, W. Chen, L. Yin, J.S. Zhu, N.W. Chen, W.X. Chen, Oleanolic acid induces apoptosis of MKN28 cells via AKT and JNK signaling pathways, Pharmaceut. Biol. 52 (2014) 789–795, https://doi.org/10.3109/13880209.2013.864683.

[16] B. Li, Y. Yang, L. Chen, S. Chen, J. Zhang, W. Tang, 18α-Glycyrrhetinic acid monoglucuronide as an anti-inflammatory agent through suppression of the NF-κB and MAPK signaling pathway, MedChemComm 8 (2017) 1498–1504, https://doi.org/10.1039/C7MD00210F.

[17] M. Bernela, M. Ahuja, R. Thakur, Enhancement of anti-inflammatory activity of glycyrrhizic acid by encapsulation in chitosan-katira gum nanoparticles, Eur. J. Pharm. Biopharm. 105 (2016) 141–147, https://doi.org/10.1016/j.ejpb.2016.06.003.

[18] D.S. Raghuvanshi, N. Verma, S. Singh, S. Luqman, A.C. Gupta, D.U. Bawankule, S. Tandon, A. Nagar, Y. Kumar, F. Khan, Design and synthesis of novel oleanolic acid based chromenes as anti-proliferative and anti-inflammatory agents, New J. Chem. 42 (2018) 16782–16794, https://doi.org/10.1039/C8NJ03564D.

[19] H.L. Alvarado, G. Abrego, M.L. Garduño-Ramirez, B. Clares, A.C. Calpena, M.L. García, Design and optimization of oleanolic/ursolic acid-loaded nanoplatforms for ocular anti-inflammatory applications, Nanomed.: Nanotechnol., Biol. Med. 11 (3) (2015) 521–530, https://doi.org/10.1016/j.nano.2015.01.004.

[20] A.T. Nelson, A.M. Camelio, K.R. Claussen, J. Cho, L. Tremmel, J. DiGiovanni, D. Siegel, Synthesis of oxygenated oleanolic and ursolic acid derivatives with anti-inflammatory properties, Bioorg. Med. Chem. Lett. 25 (2015) 4342–4346, https://doi.org/10.1016/j.bmcl.2015.07.029.

[21] D. Kashyap, A. Sharma, H.S. Tuli, S. Punia, A.K. Sharma, Ursolic acid and oleanolic acid: pentacyclic terpenoids with promising anti-inflammatory activities, Recent Patents Inflam. Allergy Drug Discov. 10 (2016) 21–33, https://doi.org/10.2174/1872213X10666160711143904.

[22] S.M. Abd El-Twab, W.G. Hozayen, O.E. Hussein, A.M. Mahmoud, 18 β-Glycyrrhetinic acid protects against methotrexate-induced kidney injury by up-regulating the Nrf2/ARE/HO-1 pathway and endogenous antioxidants, Renal Failure 38 (2016) 1516–1527, https://doi.org/10.1080/0886022X.2016.1216722.

[23] C.H. Wu, A.Z. Chen, G.C. Yen, Protective effects of glycyrrhizic acid and 18β-glycyrrhetinic acid against cisplatin-induced nephrotoxicity in BALB/c mice, J. Agric. Food Chem. 63 (2015) 1200–1209, https://doi.org/10.1021/jf505471a.

[24] C. Oprean, A. Ivan, F. Bojin, M. Cristea, C. Soica, L. Drăghia, A. Caunii, V. Paunescu, C. Tatu, Selective in vitro anti-melanoma activity of ursolic and oleanolic acids, Toxicol. Mechan. Methods 28 (2018) 148–156, https://doi.org/10.1080/15376516.2017.1373881.

[25] X.L. Bai, T.F. Lai, T. Zhou, Y.C. Li, X.T. Li, H.W. Zhang, In vitro antioxidant activities of phenols and oleanolic acid from mango peel and their cytotoxic effect on A549 cell line, Molecules 23 (2018) 1395, https://doi.org/10.3390/molecules23061395.

[26] A. Loesche, A. Köwitsch, S.D. Lucas, Z. Al-Halabi, W. Sippl, A. Al-Harrasi, R. Csuk, Ursolic and oleanolic acid derivatives with cholinesterase inhibiting potential, Bioorg. Chem. 85 (2019) 23–32, https://doi.org/10.1016/j.bioorg.2018.12.013.

[27] Y.Y. Zhong, H.S. Chen, P.P. Wu, B.J. Zhang, Y. Yang, Q.Y. Zhu, C.G. Zhang, S.Q. Zhao, Synthesis and biological evaluation of novel oleanolic acid analogues as potential α-glucosidase inhibitors, Eur. J. Med. Chem. 164 (2019) 706–716, https://doi.org/10.1038/srep45578.

[28] B.Y. Fan, B.C. Jiang, S.S. Yan, B.H. Xu, H.L. Huang, G.T. Chen, Anti-inflammatory 18β-glycyrrhetinin acid derivatives produced by biocatalysis, Planta Med. 85 (2019) 56–61, https://doi.org/10.1055/a-0662-0296.

[29] L. Jin, B. Zhang, S.X. Hua, M. Ji, X.C. Huang, R.Z. Huang, H.S. Wang, Glycyrrhetinic acid derivatives containing aminophosphonate ester species as multidrug resistance reversers that block the NF-κB pathway and cell proliferation, Bioorg. Med. Chem. Lett. 28 (2018) 3700–3707, https://doi.org/10.1016/j.bmcl.2018.10.025.

[30] M. Sahn, A. Grupe, L. Heller, H. Hussain, A. Al-Harrasi, R. Csuk, Synthesis and cytotoxicity of 3-amino-glycyrrhetinic acid derivatives, Mediterr. J. Chem. 7 (2018) 39–55, https://doi.org/10.13171/mjc71/01804111430-cesuk.

[31] R. Wang, Y. Li, X.D. Huai, Q.X. Zheng, W. Wang, H.J. Li, Q.Y. Huai, Design and preparation of derivatives of oleanolic and glycyrrhetinic acids with cytotoxic properties, Drug Des., Develop. Therapy 12 (2018) 1321–1336, https://doi.org/10.2147/DDDT.S166051.

[32] A.V. Markov, A.V. Sen'kova, M.A. Zenkova, E.B. Logashenko, Novel glycyrrhetinic acid derivative soloxolone methyl inhibits the inflammatory response and tumor growth in vivo, Mol. Biol. 52 (2) (2018) 262–268, https://doi.org/10.1134/S0026893318020073.

[33] X.H. Liu, B.L. Li, Z. Zhang, Y.J. Wei, Z.X. Xu, S.L. Qin, N. Liu, R. Zhao, J.Y. Peng, G. Yang, M. Qi, T.T. Liu, M.D. Xie, S.W. Liu, X. Gao, C. Lu, L.J. Zhu, X.Y. Long, H. Kang, T. Sun, H.G. Zhou, M.M. Wei, G. Yang, C. Yang, Synthesis and discovery novel anti-cancer stem cells compounds derived from the natural triterpenoic acids, J. Med. Chem. 61 (2018) 10814–10833, https://doi.org/10.1021/acs.jmedchem.8b01445.

[34] V. Khwaza, O. Oyedeji, B. Aderibigbe, Antiviral activities of oleanolic acid and its analogues, Molecules 23 (2018) 2300, https://doi.org/10.3390/molecules23092300.

[35] L. Jin, L. Dai, M. Ji, H. Wang, Mitochondria-targeted triphenylphosphonium conjugated glycyrrhetinic acid derivatives as potent anticancer drugs, Bioorg. Chem. 85 (2019) 179–190, https://doi.org/10.1016/j.bioorg.2018.12.036.

[36] F.H. Chu, W.X. Zhang, W.B. Guo, Z.Y. Wang, Y.Q. Yang, X.Y. Zhang, K. Fang, M.M. Yan, P.L. Wang, H.M. Lei, Oleanolic acid-amino acids derivatives: design, synthesis, and hepatoprotective evaluation in vitro and in vivo, Molecules 23 (2018) 322.

[37] P. De, M. Baltas, F. Bedos-Belval, Cinnamic acid derivatives as anticancer agents-a review, Curr. Med. Chem. 18 (2011) 1672–1703, https://doi.org/10.3390/molecules23020322.

[38] M. Hunke, W. Martinez, A. Kashyap, T. Bokoskie, M. Pattabiraman, S. Chandra, Antineoplastic actions of cinnamic acids and their dimers in breast cancer cells: a comparative study, Anticancer Res. 38 (2018) 4469–4474, https://doi.org/10.21873/anticanres.12749.

[39] P. Su, Y.L. Shi, J.F. Wang, X.X. Shen, J. Zhang, Anticancer agents derived from natural cinnamic acids, Anticancer Agents Med. Chem. 15 (2015) 980–987.