Accepted Manuscript

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PII: S0223-5234(16)30192-1

DOI: 10.1016/j.ejmech.2016.03.018

Reference: EJMECH 8443

To appear in: *European Journal of Medicinal Chemistry*

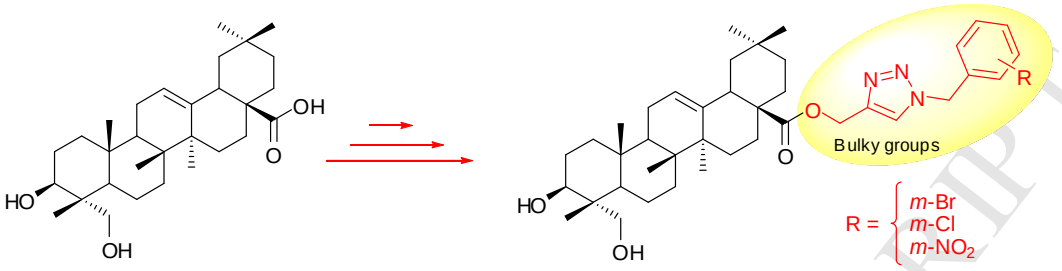
Received Date: 22 December 2015

Revised Date: 4 March 2016

Accepted Date: 5 March 2016

Please cite this article as: D. Rodríguez-Hernández, A.J. Demuner, L.C.A. Barbosa, L. Heller, R. Csuk, Novel hederagenin-triazolyl derivatives as potential anti-cancer agents, *European Journal of Medicinal Chemistry* (2016), doi: 10.1016/j.ejmech.2016.03.018.

Graphical abstract



Hederagenin

EC_{50} = 3-4.1 µM against: 518A2 (melanoma), A2780 (ovarian), HT29 (colon), A549 (lung), MCF7 (breast), 8505C (thyroid)

NOVEL HEDERAGENIN-TRIAZOLYL DERIVATIVES AS POTENTIAL ANTI-CANCER AGENTS

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Abstract:

A series of novel aryl-1*H*-1,2,3-triazol-4-yl methylester and amide derivatives of the natural product hederagenin was synthesized aiming to develop new antitumor agents, using Huisgen 1,3-dipolar cycloaddition reactions, with yields between 35% to 95%. The structures of all derivatives (**2-31**) were confirmed by MS, IR, ^{1}H NMR and ^{13}CNMR spectroscopic data. The cytotoxic activities of all compounds were screened against a panel of six human cancer cell lines using SRB assay. It was found that most of the compounds displayed higher levels of antitumor activities as compared to parent hederagenin. Compounds **4**, **8** and **15** were the most potent againstall human cancer cell lines. Furthermore, compound **11** was the most cytotoxic against cell HT29 showing EC_{50} = 1.6 µM and a selectivity index of 5.4.

Keywords: *Sapindus saponaria*; Huisgen 1,3-dipolar cycloaddition; hederagenin derivatives; SRB assay

1. Introduction

Hederagenin (**He**) is a pentacyclic oleane-type triterpenoid that exhibits anti-inflammatory [1], antifungal [2, 3], anti-leishmania [4] and antimicrobial [5, 6] activities as well as cytotoxicity to different tumor cell lines [7, 8]. This triterpenoic acid can be extracted in high quantities from the fruits of *Sapindus saponaria* L., (Sapindaceae), a tropical tree being popularly known in Brazil as "sabão-de-soldado" (soldier soap) or "saboeiro" (soap-maker) [9]. The fruits of *S. saponaria* accumulate in their pericarps great quantities of saponins carrying hederagenin as the most abundant aglycone. In addition, hederagenin acts as a chemotaxonomic marker for plants of the Sapindaceae family. Hence great interest has been aroused with the investigation of the pharmaceutical effects attributed to this natural product. It has also been reported that other families like Dipsacaceae also produce large amounts of hederagenin as aglycone of their saponins [10].

During the last few years our research groups have been working on structural modifications of natural products, in the search for more active compounds as potential pharmaceuticals or agrochemicals [11-15]. We have a special interest in utilizing terpenes largely abundant and available from several natural sources as sesquiterpenes, diterpenes and triterpenes as lead structures for new drug discovery, since many of these compounds have been reported to show important bioactivities, including anti-cancer effects [8, 13-18]. Recently, we have demonstrated that derivatives of oleanolic acid, 11-keto-β-boswellic acid, glycyrrhetinic acid maslinic acid and 23-hydroxyoleanolic acid (**He**) bearing bulky lipophilic groups attached to carbonyl-28 are amongst the most cytotoxic derivatives [8, 16-19]. Based on our previous success with hederagenin and maslinic acid, we proposed a

59 modification at position-28, by adding a triazolyl group, a well known pharmacophore.
60 Triazole containing compounds are able to bind to a variety of enzymes and receptors by
61 non-covalent interactions, hence displaying a large array of biological activities [18].
62 Several compounds of this class have found application as anti-infective, anticancer,
63 antiviral, and anti-hypertensive agents [20-22]. Recently, it has been found that triazolyl
64 derivatives of the natural pentacyclic triterpene ursolic, betulinic and oleanolic acid shows
65 cytotoxic activity against several cancer cell lines, while not affecting normal cell lines [19,
66 23-24]. Usually, the most used and effective methodology to prepare triazolyl derivatives
67 involves a [3+2] cycloaddition reaction between a terminal alkyne and an azide [25].

68 Considering, our on-going projects on the use of natural products as scaffold for the
69 discovery of new potential pharmaceutical and agrochemical compounds [8, 26-28]
70 besides, the addition of a bulky group substituent at the C-28 of **He** can enhance its
71 anticancer potential, herein we report the preparation of a library of novel 1,2,3-triazolyl
72 derivatives of hederagenin bound to the C-28 and their cytotoxic profiles against several
73 cancer cell lines were evaluated.

74 **2. Results and discussion**

75 *2.1. Chemistry*

76 Hederagenin (**He**) has been recently reported to show low cytotoxic properties for several
77 human cancer cell lines with EC_{50} > 30 µM [8]. This compound, however, offers several
78 hot spots (e.g. C-3, C-12, C-23 and C-28) to provide enough space for chemical
79 modifications. We have undertaken a research program directed towards the structural

modifications of hederagenin at its C-28 position, supported by previous reports that showed derivatives holding bulky groups attached to C-28 to modulate the cytotoxic activity for this class of compounds for several cancer cell lines [8, 16]. The preparation of 1,2,3-triazolyl derivatives of hederagenin was completed by a Huisgen 1,3-dipolar cycloaddition. Firstly, hederagenin (**He**) was isolated from the pericarp of *S. saponaria* as previously described [8, 29]. Subsequently, a (prop-2-yn-1-yl) hederageninester (**1a)** was prepared (92% yield) by a reaction of **He** with propargyl bromide in the presence of finely grounded potassium carbonate in *N*,*N*-dimethylformamide (DMF) [8]. In addition, a (prop-2-yn-1-yl) hederagenin-amide (**1b**) was also obtained in excellent yields (93%) by reacting **He** with 2-propynylamine in the presence of *O*-(benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium- tetrafluoroboratetetrabutyl (TBTU) as a coupling catalystand *N*,*N*-diisopropylethylamine (DIPEA) as a base (Scheme1) [8].

[Insert Scheme1]

Benzyl azides were prepared from their respective benzylbromides with sodium azide in DMF (Scheme 2) [30]. The azides were obtained in excellent yields (94-97%) and were used without further purification.

[Insert Scheme2]

1,3-Dipolar cycloaddition reaction of **1a** or **1b** with benzyl azides in presence of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate resulted into the formation of 1,4-substitutedtriazolyl derivatives **2-31**.The overall chemical yields of the synthesized compounds ranged from 35% to 95% (Scheme3) [25].

[Insert Scheme 3]

The structures of the triazolyl derivatives (**2-31)** were confirmed by extensive spectroscopic analyses. All compounds showed in their respective IR spectra typical absorptions expected for the major functional groups present. For example, the stretch vibration of the ester C=O was detected as a strong absorption band located between $\bar{\upsilon}$ = 1720-1735 cm^{-1} for **2-16** together with absorptions between $\bar{\upsilon}$ =1250-1150 cm^{-1} due to stretching of C-CO-O. For amides **17-31** the C=O stretch vibrational bands were observed in the range of $\bar{\upsilon}$ = 1640-1620 cm^{-1} [31].

In the ^{1}H NMR spectra, the formation of the heterocyclic unit was confirmed by the signal around δ = 7.48-7.72 corresponding to H-33 of the triazole ring. In addition, the signals of the aromatic hydrogen atoms were detected between δ = 6.80 and 8.22. For the amides the signals for the NH group were observed at δ = 6.58-6.65 each as a triplet (J = 5.0±0.6 Hz). All ^{13}C NMR signals for the triterpenoic skeleton in this series of compounds were similar to the parent hederagenin with exception of the signals for C-28 and the group attached at this position. For carbon C-28 a shift to higher field for the esters and amides was observed as compared to parent **He** (δ =180.7 for **He** to δ =177.4±0.4 for the esters carbonyl and to δ = 178±0.4 for the amide carbonyl). A detailed assignment of the NMR spectra (^{1}H and ^{13}C) for all compounds is presented in the supplementary material associated to this paper. The assignments were possible by means of 2D NMR techniques when required, and the data were fully consistent with the proposed structures.

2.2. Biological screening

The cytotoxic activity of the novel hederagenin derivatives (**2-31**) was evaluated employing six human tumour cell lines (melanoma cells - 518A2; ovarian carcinoma - A2780; colon adenocarcinoma - HT29; breast adenocarcinoma - MCF7; lung cancer - A549; thyroid carcinoma - 8505C) and non-malignant mouse fibroblasts (NIH 3T3), using the well-established photometric sulforhodamine B assay (SRB) [32]. The results of these assays are summarized in Table 1.

[Insert Table 1]

In general, conversion of parent **He** into esters and amides bearing a 1,2,3-triazole unit resulted in an increase of cytotoxicity. As shown forvirtually all human cancer cell lines, ester substituted compounds bearing a 1,2,3-triazolyl group showed higher cytotoxicity than parent hederagenin (Table 1; Fig. S1). The only exception is compound **14** that presented EC_{50} > 30 µM in 8505C (thyroid cell line), comparable to parent hederagenin. In the case of amide derivatives, all compounds (**17-31**) were more active than **He** against the cell lines A2780, HT29, MCF7. For the cell lines 518A2 and A549 most amide derivatives were more active than **He** (Table 1; Fig. S2). However, for the thyroid cell line (8505C) only compound **25-28** were more active compared to **He**. These results indicate that the presence of a bulky group bonded to carbonyl-28 of the triterpene skeleton modulates their cytotoxic activity. Similar results have previously been observed for hederagenin (**He**), when in its natural form (free acid) a 20-fold lower cytotoxicity was observed as compared to the corresponding ester and amide derivatives [8]. 1,2,3-Triazolyl compounds having an ester group are generally more cytotoxic than compounds carrying an amide moiety. Hence, we assumed that the improvements may be the result either of a

different transport mechanisms of the compounds through the membrane or of a different integration into the cell membrane [33-34].

For human cell line MCF-7 (breast adenocarcinoma), all derivatives (**2-31**) showed cytotoxic activity at 10 µM or at lower dose, (Table 1). For the human cell line HT29 (colon adenocarcinoma), the activity of the *ortho* substituted compounds (**3**, **18**, **9**, **24**, **11** and **26**) decreased with the atomic radius of the halogen substituent (Fig. 1). In addition, the *ortho*-fluorobenzyl-1,2,3-triazolyl ester **11** was the most active compound against this cell line showing EC_{50} = 1.6 µM. This compound (**11**) also exhibited some selectivity (SI= 5.4; SI is defined as the quotient of EC_{50} values according to $EC_{50\ [NIH\ 3T3]}/EC_{50\ [tumor\ cell\ line]}$) in cytotoxicity discriminating between the cancer cell line HT29 and non-malignant mouse fibroblasts NIH 3T3. Moreover, the 1,2,3-triazol benzyl ester **2** (EC_{50} = 2.8 µM) also gave a good selectivity (SI = 4.2) between the cancer cell line HT29 and non-malignant mouse fibroblasts NIH 3T3 (Table S2).

[Insert Figure 1]

The ester derivatives **4**, **8** and **15** possessing a *m*-bromo, *m*-chloro and *m*-nitro substituent were the most active compounds against all human cell lines tested so far, showing EC_{50} values ranging between 3.2-4.0 µM for **4**, between 3.1-4.0 µM for **8** and between 3.2-4.1 µM for **15** (Fig.2). These results revealed that these compounds (**4**, **8** and **15**) are at least ~8 times more active than parent hederagenin (Table 1, Fig. 2); however, they were not selective between malignant and non-malignant cells (Table S2).

[Insert Figure 2]

3. Conclusion

In summary, a series of novel aryl-1*H*-1,2,3-triazol-4-yl-methyl ester and amide derivatives of hederagenin has been synthesized by employing Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition reactions of terminal alkyne derivatives of **He** with various benzyl azides. Compared to hederagenin most compounds exhibited higher cytotoxicity against all tested cancer cell lines. The ester derivatives were more cytotoxic than the amides. Furthermore, esters **4**, **8** and **15** were the most active derivatives towards all cell lines tested, showing EC_{50}in the range of 3.0-4.1 µM. On the other hand, compounds **2** and **11** were the most cytotoxic against the colon cancer cell (HT29) with EC_{50} = 2.8 µM and 1.6 µM, respectively. In addition, compound **11** showed some selectivity for the cancer cell line HT29 and was less toxic for non-malignant mouse fibroblasts NIH 3T3 displaying SI = 5.4.

4. Experimental part

4.1. General procedures.

Reagents were procured from Sigma-Aldrich (Milwaukee, Wisconsin, USA) and were used without any purification. Solvents were supplied by Vetec (Rio de Janeiro, Brazil). Analytical thin layer chromatography (TLC) were performed on silica gel 60 F_{254} 0.2 mm thick plates (supplied by Merck, Rio de Janeiro, Brazil) and were visualized under UV-B light or by spraying with phosphomolybdic acid in 10% ethanol, followed by heating. Flash column chromatography (typical size of 20 cm length and 2 cm of diameter) was performed using silica gel 230-400 mesh. All compounds were fully characterized by IR, EI-MS, ^{1}H

NMR and ^{13}C NMR spectroscopy. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR spectrophotometer, preparing the samples as potassium bromide disks (1% w/w). Mass spectra were recorded on a Shimadzu GCMS-QP5050A instrument by direct insertion, using EI mode (70 eV). High resolution mass spectra were recorded on a Bruker Micro TOF (resolution = 10,000 FWHM) under electro spray ionization (ESI) and the results are reported to four decimal figures. Elemental analyses were measured on a Foss-Heraeus Vario EL unit. The ^{1}H and ^{13}C-NMR spectra were recorded on a Varian Mercury 300 spectrometer at 300 and 75 MHz, respectively, using $CDCl_3$ as solvent and TMS as internal reference, unless otherwise stated. Melting points were measured on a MQAPF-301 apparatus and were not corrected.

The ^{1}H NMR spectra for all compound were assigned for the signals that were clearly well defined as described for each compound, For all compounds a multiplet was observed in the range of 0.5 to 2.5 ppm, so the hydrogen atoms in such range could not be assigned.

*4.2 Hederagenin (**He**).*

He was isolated from pericarp of *Sapindus saponaria* L., as previously reported [8], and it was obtained as a white solid; m.p. 318-320 ^{o}C (lit.: 317-320 ^{o}C [29]); R_f = 0.24 (hexane/ethyl acetate, 1:1 v/v). All spectroscopic data (IR, MS and NMR) were in agreement with the literature [35-37].

*4.3 Procedure for the preparation of compounds **1a** and **1b.***

Compounds **1a** and **1b** were synthesized using methods previously published [8].

206 *4.4 General procedure for synthesis of benzyl azides (**a-o**).*

207 The benzyl azides were preparedfrom the reaction of a solution of the appropriate benzyl
208 bromide (0.24 mmol) in DMF (10 mL) with sodium azide (25 mg; 0.38 mmol); in short, the
209 reaction mixture was stirred for 2 h at room temperature until TLC analyses revealed the
210 consumption of the starting material. The mixture was poured into water (50 mL), extracted
211 with diethyl ether (2x30 mL), washed with brine (3x20 mL), dried over Na_2SO_4, filtered,
212 and the filtrate was concentrated in a rotary evaporator under reduced pressure to afford the
213 benzyl azides (**a-o**). Since TLC analysis of the crude products revealed only one spot, they
214 were used without further purification.

215 *4.5 General procedure for synthesis of compounds (**2-31**).*

216 To a solution ofalkynes**1a** or **1b** (0.15 mmol) and the appropriate azide (0.30 mmol) in
217 CH_2Cl_2 (5 mL) and H_2O (5 mL) $CuSO_4{\cdot}5H_2O$ (63 mg; 0.25 mmol) and Na-L-ascorbate
218 (100 mg; 0.5 mmol) were added. This reaction mixture was stirred vigorously for 24h at
219 room temperature, until TLC analysis revealed a total consumption of the starting material.
220 The mixture was diluted with H_2O (20 mL), extracted with CH_2Cl_2 (3 x 20 mL). The
221 combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered,
222 and the solvent was removed in a rotary evaporator under reduced pressure to afford the
223 crude product. This product was purified by column chromatography (silica gel,
224 hexane/ethyl acetate, 2:1 v/v) to yield the target compounds **2-31**each as a solid material.

225 *4.5.1 (Benzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-oate (**2**).*

White solid; yield: 65mg, 60%; m.p. 101-102.8°C; R_f = 0.45 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3420, 3148, 3064, 1724, 1160, 1048, 1008, 722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.47 (s, 1H, H-33), 7.35 (brs, 3H), 7.26 (brs, 2H), 5.51 (d, 1H, J = 15.0 Hz, H-34_a), 5.45 (d, 1H, J = 15.0 Hz, H-34_b), 5.21 (brs, 1H, H-12), 5.13 (brs, 2H, H-31), 3.71 (d, 1H, J = 10.3 Hz, H-23_a), 3.62 (brt, 1H, J = 8.0 Hz, H-3), 3.40 (d, 1H, J = 9.6 Hz, H-23_b), 2.78 (brdd, 1H, J = 13.3 Hz, H-18), 1.08 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.86 (s, 6H, 2xCH_3), 0.50 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.81 (C-28), 143.71 (C-13), 134.32 (C-32), 131.04 (C-35), 129.26 (C-37), 129.26 (C-37'), 128.97 (C-38), 128.22 (C-37'), 128.22 (C-37), 123.03 (C-12), 122.44 (C-33), 76.91 (C-3), 72.18 (C-23), 57.61 (C-31), 54.31 (C-34), 49.88 (C-9), 47.64 (C-17), 46.81 (C-5), 45.96 (C-19), 41.90 (C-4), 41.83 (C-14), 41.37 (C-18), 39.38 (C-8), 38.22 (C-1), 37.01 (C-10), 33.92 (C-21), 33.17 (C-29), 32.55 (C-7), 32.41 (C-22), 30.76 (C-20), 27.72 (C-15), 26.82 (C-27), 25.93 (C-2), 23.71 (C-30), 23.45 (C-11), 23.06 (C-16), 18.61 (C-6), 16.84 (C-26), 15.85 (C-25), 11.57 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{58}N_3O_4]^+$: 644.4427, found: 644.4424; CHN calcd.: C, 74.61; H, 8.92; N, 6.52; found: C, 74.48; H, 9.07; N, 6.39.

*4.5.2 (o-Bromobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-oate (**3**).*

White solid; yield: 110mg, 91%; m.p. 94.8-96.3 °C; R_f = 0.44 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3408, 3154, 3068, 1722, 1160, 1046, 1030, 1008, 750, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, 1H, J = 7.8 Hz, H-37), 7.57 (s, H, H-33), 7.23 (m, H-38, H-39, H-40), 5.62 (t, 2H, J = 16.3 Hz H-34), 5.22 (brs, 1H, H-12), 5.14 (s, 2H, H-31), 3.70

(d, 1H, J = 10.2 Hz, H-23$_a$), 3.61 (brt, 1H, J = 8.0 Hz, H-3), 3.39 (d, 1H, J = 10.2 Hz, H-23$_b$), 2.79 (brdd, 1H, J = 11.2 Hz, H-18), 1.08 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.87 (s, 9H, 3xCH_3), 0.52 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.77 (C-28), 143.68 (C-13), 143.62 (C-32), 134.00 (C-35), 133.39 (C-37), 130.63 (C-40), 130.58 (C-39), 128.30 (C-38), 124.68 (C-12), 123.69 (C-36), 122.45 (C-33), 76.85 (C-3), 72.10 (C-23), 57.58 (C-31), 53.95 (C-34), 49.86 (C-9), 47.63 (C-17), 46.80 (C-5), 45.93 (C-19), 41.87 (C-4), 41.81 (C-14), 41.36 (C-18), 39.37 (C-8), 38.21 (C-1), 36.99 (C-10), 33.91 (C-21), 33.15 (C-29), 32.53 (C-7), 32.41 (C-22), 30.75 (C-20), 27.71 (C-15), 26.75 (C-27), 25.92 (C-2), 23.70 (C-30), 23.46 (C-11), 23.04 (C-16), 18.60 (C-6), 16.86 (C-26), 15.83 (C-25), 11.58 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{57}BrN_3O_4]^+$: 722.3532, found: 722.3520; CHN calcd.: C, 66.47; H, 7.81; N, 5.81; found: C, 66.30; H, 7.98; N, 5.62.

*4.5.3 (m-Bromobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-oate (**4**).*

White solid; yield: 78 mg, 65%; m.p. 125.4-125.6 ^oC; R_f = 0.44 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3414, 3148, 3094, 1718, 1160, 1048,1008, 772, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (s, H, H-33), 7.47 (d, 1H, J = 7.7 Hz, H-38), 7.39 (s, 1H, H-36), 7.24 (d, H, J = 7.7 Hz, H-40), 7.18 (t, H, J = 7.5 Hz, H-39), 5.45 (t, 2H, J = 17.7 Hz, H-34), 5.21 (brs, 1H, H-12), 5.14 (s, 2H, H-31), 3.70 (d, 1H, J = 10.3 Hz, H-23$_a$), 3.61 (brt, 1H, J = 8.0 Hz, H-3), 3.40 (d, 1H, J = 10.2 Hz, H-23$_b$), 2.79 (brdd, 1H, J = 11.0 Hz, H-18), 1.08 (s, 3H, CH_3), 0.89 (s, H, CH_3), 0.87 (s, 9H, 3xCH_3), 0.50 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.85 (C-28), 143.89 (C-13), 143.66 (C-32), 136.69 (C-35), 131.13 (C-38), 131.12 (C-36), 130.79 (C-39), 126.66 (C-40), 124.11 (C-12), 123.25 (C-37), 122.45

(C-33), 76.89 (C-3), 72.15 (C-23), 57.56 (C-31), 53.47 (C-34), 49.87 (C-9), 47.62 (C-17), 46.82 (C-5), 45.94 (C-19), 41.88 (C-4), 41.83 (C-14), 41.38 (C-18), 39.38 (C-8), 38.21 (C-1), 36.99 (C-10), 33.91 (C-21), 33.16 (C-29), 32.55 (C-7), 32.41 (C-22), 30.75 (C-20), 27.71 (C-15), 26.73 (C-27), 25.92 (C-2), 23.71 (C-30), 23.44 (C-11), 23.07 (C-16), 18.60 (C-6), 16.84 (C-26), 15.84 (C-25), 11.59 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{57}BrN_3O_4]^+$: 722.3532, found: 722.3522; CHN calcd.: C, 66.47; H, 7.81; N, 5.81; found: C, 66.32; H, 8.02; N, 5.61.

*4.5.4 (p-Bromobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-oate (**5**).*

White solid; yield: 109 mg, 91%; m.p. 111.6-112.3 ^oC; R_f = 0.44 (hexane/ethyl acetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3420, 3150, 3056, 1722, 1160, 1048, 1012, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.48 (m, 3H, H-33, H-37, H-37'), 7.12 (d, 2H, J = 8.1 Hz, H-36, H-36'), 5.43 (t, 2H, J =13.4 Hz, H-34), 5.21 (brs, 1H, H-12), 5.13 (s, 2H, H-31), 3.70 (d, 1H, J = 10.2 Hz, H-23_a), 3.61 (brt, 1H, J = 7.9 Hz, H-3), 3.40 (d, 1H, J = 10.2 Hz, H-23_b), 2.79 (brdd, 1H, J = 13.0, 2.3 Hz, H-18), 1.08 (s, 3H, CH_3), 0.87 (s, 12H, 4xCH_3), 0.49 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.84 (C-28), 143.91 (C-13), 143.68 (C-32), 133.53 (C-35), 132.43 (C-37, C-37'), 129.77 (C-36, C-36'), 123.96 (C-12), 123.16 (C-38),122.43 (C-33), 76.87 (C-3), 72.12 (C-23), 57.57 (C-31), 53.56 (C-34), 49.86 (C-9), 47.61 (C-17), 46.82 (C-5), 45.93 (C-19), 41.88 (C-4), 41.82 (C-14), 41.36 (C-18), 39.37 (C-8), 38.20 (C-1), 36.98 (C-10), 33.90 (C-21), 33.15 (C-29), 32.54 (C-7), 32.41 (C-22), 30.75 (C-20), 27.70 (C-15), 26.78 (C-27), 25.92 (C-2), 23.69 (C-30), 23.42 (C-11), 23.07 (C-16), 18.57 (C-6), 16.85 (C-26), 15.81 (C-25), 11.59 (C-24); HRMS (ESI TOF-MS)

292 $[M+H]^+$calcd. for $[C_{40}H_{57}BrN_3O_4]^+$: 722.3532, found: 722.3526; CHN calcd.: C, 66.47; H,
293 7.81; N, 5.81; found: C, 66.29; H, 7.92; N, 5.69.

294 *4.5.5 (2,6-Dichlorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-*
295 *28-oate (**6**).*

296 White solid; yield: 100mg, 84%; m.p. 113-114.6 ^oC; R_f = 0.45 (hexane/ethylacetate 1:1
297 v/v); IR (KBr): $\bar{\upsilon}$ = 3420, 3154, 3086, 1718, 1160, 1046, 764, 732 cm^{-1}; ^1H NMR (300
298 MHz, $CDCl_3$): δ = 7.49 (s, 1H, H-33), 7.38 (d, 2H, *J* = 7.5 Hz, H-37, H-39), 7.30 (d, 1H, *J*
299 = 8.3 Hz, H-38), 5.81 (s, 2H, H-31), 5.20 (brs, 1H, H-12), 5.14 (d, 1H, *J* = 12.7 Hz, H-34_a),
300 5.08 (d, 1H, *J* = 12.7 Hz, H-34_b), 3.69 (d, 1H, *J* = 10.2 Hz, H-23_a), 3.61 (brt, 1H, *J* = 7.9
301 Hz, H-3), 3.38 (d, 1H, *J* = 10.2 Hz, H-23_b), 2.78 (brdd, 1H, *J* = 11.0 Hz, H-18), 1.07 (s,
302 3H, CH_3), 0.89 (s, 3H, CH_3), 0.86 (s, 9H, 3xCH_3), 0.48 (s, 3H, CH_3); ^{13}C NMR (75 MHz,
303 $CDCl_3$): δ = 177.77 (C-28), 143.71 (C-13), 143.20 (C-32), 136.91 (C-35), 131.26 (C-36),
304 129.96 (C-40), 129.02 (C-37), 129.02 (C-39), 129.02 (C-38), 123.77 (C-12), 122.41 (C-33),
305 76.83 (C-3), 72.08 (C-23), 57.53 (C-31), 49.86 (C-9), 49.16 (C-34), 47.62 (C-17), 46.78
306 (C-5), 45.92 (C-19), 41.84 (C-4), 41.79 (C-14), 41.34 (C-18), 39.34 (C-8), 38.21 (C-1),
307 36.98 (C-10), 33.90 (C-21), 33.14 (C-29), 32.51 (C-7), 32.40 (C-22), 30.74 (C-20), 27.68
308 (C-15), 26.70 (C-27), 25.92 (C-2), 23.66 (C-30), 23.45 (C-11), 22.99 (C-16), 18.58 (C-6),
309 16.73 (C-26), 15.82 (C-25), 11.59 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for
310 $[C_{40}H_{55}Cl_2N_3O_5]^+$: 712.3648, found: 712.3632; CHN calcd.: C, 65.92; H, 7.61; N, 5.77;
311 found: C, 65.77; H, 7.81; N, 5.54.

*4.5.6 (p-Chlorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-oate (**7**).*

White solid; yield: 39 mg, 33%; m.p. 169.3-170.2 ^{o}C; R_f = 0.45 (hexane/ethylacetate 1:1 v/v); IR (KBr): ῡ = 3412, 3150, 3100, 1722, 1160, 1048, 1016 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1H, H-33), 7.33 (d, 2H, *J* = 8.2 Hz, H-37, H-37'), 7.19 (d, 2H, *J* = 8.2 Hz, H-36, H-36'), 5.45 (t, 2H, *J* = 16.6 Hz, H-34), 5.21 (brs, 1H, H-12), 5.13 (s, 2H, H-31), 3.71 (d, 1H, *J* = 10.2 Hz, H-23$_a$), 3.61 (brt, 1H, *J* = 8.2 Hz, H-3), 3.40 (d, 1H, *J* = 10.2 Hz, H-23$_b$), 2.78 (brdd, 1H, *J* = 13.0 Hz, H-18), 1.08 (s, 3H, CH_3), 0.87 (s, 12H, 4xCH_3), 0.49 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.86 (C-28), 143.92 (C-13), 143.70 (C-32), 135.06 (C-35), 133.04 (C-38), 129.52 (C-36, C-36'), 129.49 (C-37, C-37'), 123.98 (C-12), 122.44 (C-33), 76.91 (C-3), 72.18 (C-23), 57.60 (C-31), 53.53 (C-34), 49.87 (C-9), 47.63 (C-17), 46.83 (C-5), 45.95 (C-19), 41.91 (C-4), 41.84 (C-14), 41.38 (C-18), 39.38 (C-8), 38.21 (C-1), 36.99 (C-10), 33.92 (C-21), 33.16 (C-29), 32.56 (C-7), 32.43 (C-22), 30.77 (C-20), 27.72 (C-15), 26.84 (C-27), 25.93 (C-2), 23.69 (C-30), 23.44 (C-11), 23.08 (C-16), 18.58 (C-6), 16.85 (C-26), 15.81 (C-25), 11.52 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{56}ClN_3O_4]^+$: 678.4038, found: 678.4029; CHN calcd.: C, 70.82; H, 8.32; N, 6.19; found: C, 70.59; H, 8.42; N, 6.07.

*4.5.7 (m-Chlorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-oate (**8**).*

White solid; yield: 106 mg, 90%; m.p. 111.9-113.3 ^{o}C; R_f = 0.49 (hexane/ethylacetate 1:1 v/v); IR (KBr): ῡ = 3412, 3148, 3083, 1722, 1160, 1048, 1008, 772, 734 cm^{-1}; ^{1}H NMR

(300 MHz, $CDCl_3$): δ = 7.51 (s, 1H, H-33), 7.27 (m, 3H, H-36, H-38, H-39), 7.12 (d, 1H, *J* = 6.6 Hz, H-40), 5.45 (t, 2H, *J* = 16.2 Hz, H-34), 5.21 (brs, 1H, H-12), 5.13 (s, 2H, H-31), 3.70 (d, 1H, *J* = 10.4 Hz, H-23_a), 3.61 (brt, 1H, *J* = 7.6 Hz, H-3), 3.39 (d, 1H, *J* = 10.4 Hz, H-23_b), 2.79 (brdd, 1H, *J* = 13.7 Hz, H-18), 1.08 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.86 (s, 9H, 3xCH_3), 0.50 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.84 (C-28), 143.92 (C-13), 143.65 (C-32), 136.44 (C-35), 135.17 (C-37), 130.52 (C-39), 129.18 (C-36), 128.20 (C-38), 126.18 (C-40), 124.12 (C-12), 122.44 (C-33), 76.85 (C-3), 72.09 (C-23), 57.54 (C-31), 53.85 (C-34), 49.85 (C-9), 47.60 (C-17), 46.81 (C-5), 45.92 (C-19), 41.86 (C-4), 41.82 (C-14), 41.36 (C-18), 39.37 (C-8), 38.20 (C-1), 36.98 (C-10), 33.89 (C-21), 33.14 (C-29), 32.54 (C-7), 32.40 (C-22), 30.74 (C-20), 27.69 (C-15), 26.74 (C-27), 25.91 (C-2), 23.69 (C-30), 23.42 (C-11), 23.05 (C-16), 18.58 (C-6), 16.82 (C-26), 15.82 (C-25), 11.58 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{56}ClN_3O_4]^+$: 678.4038, found: 678.4033; CHN calcd.: C, 70.82; H, 8.32; N, 6.19; found: C, 70.64; H, 8.47; N, 6.03.

*4.5.8 (o-Chlorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-oate (**9**).*

White solid; yield: 64 mg, 54%; m.p. 108.6-110.2 ^{o}C; R_f = 0.44 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3410, 3156, 3072, 1724, 1160, 1048, 1008, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (s, 1H, H-33), 7.42 (d, 1H, *J* = 7.5 Hz, H-37), 7.25 (m, 3H, H-38, H-39, H-40), 5.62 (t, 2H, *J* = 16.0 Hz H-34), 5.22 (brs, 1H, H-12), 5.14 (s, 2H, H-31), 3.71 (d, 1H, *J* = 10.1 Hz, H-23_a), 3.62 (brt, 1H, *J* = 8.1 Hz, H-3), 3.40 (d, 1H, *J* = 10.1 Hz, H-23_b), 2.80 (brdd, 1H, *J* = 10.3 Hz, H-18), 1.08 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.87 (s, 9H, 3xCH_3), 0.53 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.79 (C-28), 143.70 (C-13),

143.64 (C-32), 133.71 (C-35), 132.33 (C-36), 130.59 (C-40), 130.48 (C-37), 130.11 (C-38), 127.72 (C-39), 124.27 (C-12), 122.46 (C-33), 76.92 (C-3), 72.19 (C-23), 57.61 (C-31), 51.56 (C-34), 49.88 (C-9), 47.65 (C-17), 46.82 (C-5), 45.96 (C-19), 41.91 (C-4), 41.83 (C-14), 41.38 (C-18), 39.39 (C-8), 38.22 (C-1), 37.01 (C-10), 33.93 (C-21), 33.17 (C-29), 32.55 (C-7), 32.42 (C-22), 30.77 (C-20), 27.73 (C-15), 26.83 (C-27), 25.94 (C-2), 23.71 (C-30), 23.47 (C-11), 23.06 (C-16), 18.61 (C-6), 16.86 (C-26), 15.83 (C-25), 11.56 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{56}ClN_3O_4]^+$: 678.4038, found: 678.4026; CHN calcd.: C, 70.82; H, 8.32; N, 6.19; found: C, 70.69; H, 8.58; N, 6.09.

*4.5.9 (2,4-Difluorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-oate (**10**).*

White solid; yield: 101mg, 89%; m.p.104.5-106.2 ^oC; R_f = 0.46 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3420, 3154, 3084, 1724, 1508, 1160, 1048, 972, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.56 (s, 1H, H-33), 7.28 (m, 1H, H-40), 6.87 (m, 2H, H-37, H-39), 5.49 (t, 2H, *J* =15.1 Hz, H-34), 5.22 (brs, 1H, H-12), 5.12 (s, 2H, H-31), 3.69 (d, 1H, *J* = 10.2 Hz, H-23_a), 3.61 (brt, 1H, *J* = 7.9 Hz, H-3), 3.39 (d, 1H, *J* = 10.2 Hz, H-23_b), 2.79 (brdd, 1H, *J* = 13.1 Hz, H-18), 1.08 (s, 3H, CH_3), 0.89(s, 3H, CH_3), 0.86 (s, 9H, 3xCH_3), 0.48 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.82 (C-28), 163.47 (dd, *J* = 250.3, 11.9 Hz, C-38), 160.85 (dd, *J* = 248.9, 11.7 Hz, C-36), 143.81 (C-13), 143.66 (C-32), 131.83 (dd, *J* = 9.8, 4.7 Hz, C-40), 124.08 (C-12), 122.46 (C-33), 117.92 (dd, *J* = 15.0, 4.0 Hz, C-35), 112.31 (dd, *J* = 21.2, 3.6Hz, C-39), 104.54 (t, *J* = 25.2 Hz, C-37), 76.81 (C-3), 72.04 (C-23), 57.51 (C-31), 49.84 (C-9), 47.61 (C-17), 47.23 (d, *J* = 3.6 Hz, C-34), 46.81 (C-5), 45.93 (C-19), 41.86 (C-4), 41.81 (C-14), 41.36 (C-18), 39.35 (C-8), 38.21 (C-1),

377 36.97 (C-10), 33.91 (C-21), 33.14 (C-29), 32.54 (C-7), 32.41 (C-22), 30.74 (C-20), 27.69
378 (C-15), 26.72 (C-27), 25.92 (C-2), 23.67 (C-30), 23.43 (C-11), 23.05 (C-16), 18.55 (C-6),
379 16.75 (C-26), 15.78 (C-25), 11.57 (C-24);HRMS (ESI TOF-MS) $[M+H]^+$calcd. for
380 $[C_{40}H_{55}F_2N_3O_4]^+$: 680.4239, found: 680.4233; CHN calcd.: C, 76.03; H, 8.77; N, 6.65;
381 found: C, 75.85; H, 8.91; N, 6.47.

382 *4.5.10 (o-Fluorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-*
383 *oate (**11**).*

384 White solid; yield: 94mg, 85%; m.p. 142.3-143.6 ^oC; R_f = 0.46 (hexane/ethylacetate 1:1
385 v/v); IR (KBr): ῡ = 3412, 3150, 3098, 1732, 1234, 1158, 758 cm^{-1}; ^1H NMR (300 MHz,
386 $CDCl_3$): δ = 7.56 (s, 1H, H-33), 7.35 (m, 1H, H-40), 7.26 (m, 1H, H-38), 7.11 (m, 2H, H-
387 37, H-39), 5.54 (t, 2H, *J* = 15.5 Hz, H-34), 5.22 (brs, 1H, H-12), 5.13 (s, 2H, H-31), 3.70
388 (d, 1H, *J* = 10.3 Hz, H-23_a), 3.61 (brt, 1H, *J* = 7.9 Hz, H-3), 3.39 (d, 1H, *J* = 10.2 Hz, H-
389 23_b), 2.79 (brdd, 1H, *J* = 12.6 Hz, H-18), 1.08 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.87 (s, 9H,
390 3xCH_3), 0.50 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.79 (C-28), 160.67 (d, *J* =
391 246.6 Hz, C-36), 143.70 (C-13), 143.67 (C-32), 131.14 (d, *J* = 32.6 Hz, C-40), 130.74 (d, *J*
392 = 3.8 Hz, C-38), 124.69 (d, *J* = 3.6 Hz, C-35), 124.12 (C-12), 122.46 (C-33), 121.76 (d, *J* =
393 14.5 Hz, C-39), 115.98 (d, *J* = 20.9 Hz, C-37), 76.86 (C-3), 72.10 (C-23), 57.51 (C-31),
394 49.86 (C-9), 47.63 (C-17), 47.23 (d, *J* = 3.6 Hz, C-34), 46.80 (C-5), 45.93 (C-19), 41.87
395 (C-4), 41.87 (C-14), 41.36 (C-18), 39.36 (C-8), 38.22 (C-1), 36.98 (C-10), 33.91 (C-21),
396 33.15 (C-29), 32.53 (C-7), 32.39 (C-22), 30.75 (C-20), 27.69 (C-15), 26.75 (C-27), 25.92
397 (C-2), 23.60 (C-30), 23.43 (C-11), 23.05 (C-16), 18.58 (C-6), 16.77 (C-26), 15.80 (C-25),

11.58 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{56}FN_3O_4]^+$: 662.4333, found: 662.4325; CHN calcd.: C, 72.58; H, 8.53; N, 6.35; found: C, 70.46; H, 8.60; N, 6.03.

*4.5.11 (2,6-Difluorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-oate (**12**).*

White solid; yield: 76 mg, 67%; m.p. 108.6-110.1 ^oC; R_f = 0.44 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3418, 3150, 3074, 1724, 1628, 1160, 1036, 802, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.57 (s, 1H, H-33), 7.36 (m, 1H, H-38), 6.96 (m, 2H, H-37, H-39), 5.58 (t, 2H, *J* = 15.6 Hz, H-34), 5.22 (brs, 1H, H-12), 5.12 (s, 2H, H-31), 3.70 (d, 1H, *J* =10.1 Hz, H-23_a), 3.61 (brt, 1H, *J* = 7.8 Hz, H-3), 3.39 (d, 1H, *J* = 10.1 Hz, H-23_b), 2.80 (brdd, 1H, *J* = 12.7 Hz, H-18), 1.08 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.87 (s, 9H, 3xCH_3), 0.49 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.80 (C-28), 161.48 (dd, *J* = 249.2, 6.8 Hz, C-36, C-40), 143.69 (C-13), 143.56 (C-32), 131.64 (t, *J* = 10.1 Hz, C-38), 124.01 (C-12), 122.46 (C-33), 111.96 (m, C-37, C-39), 110.67 (t, *J* = 18.5 Hz, C-35), 76.91 (C-3), 72.17 (C-23), 57.52 (C-31), 49.89 (C-9), 47.64 (C-17), 46.80 (C-5), 45.96 (C-19), 41.87 (C-4), 41.81 (C-14), 41.49 (t, *J* = 4 Hz, C-34), 41.37 (C-18), 39.36 (C-8), 38.22 (C-1), 36.99 (C-10), 33.92 (C-21), 33.16 (C-29), 32.54 (C-7), 32.41 (C-22), 30.76 (C-20), 27.69 (C-15), 26.77 (C-27), 25.93 (C-2), 23.69 (C-30), 23.44 (C-11), 23.05 (C-16), 18.58 (C-6), 16.67 (C-26), 15.79 (C-25), 11.57 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{55}F_2N_3O_4]^+$: 680.4239, found: 680.4232; CHN calcd.: C, 76.03; H, 8.77; N, 6.65; found: C, 75.87; H, 8.91; N, 6.50.

418 *4.5.12 (p-Fluorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-*
419 *oate (**13**).*

420 White solid; yield: 85 mg, 77%; m.p. 111.3-112.6 ^{o}C; R_f = 0.46 (hexane/ethylacetate 1:1
421 v/v); IR (KBr): ῡ = 3420, 3152, 3080, 1722, 1512, 1228, 1160, 1048, 732 cm^{-1}; ^{1}H NMR
422 (300 MHz, $CDCl_3$): δ = 7.47 (s, 1H, H-33), 7.25 (m, 2H, H-36, H-36'), 7.04 (m, 2H, H-37.
423 H-37'), 5.48 (d, 1H, *J* = 15.0 Hz, H-34_a), 5.42 (d, 1H, *J* = 15.0 Hz, H-34_b), 5.21 (t, 1H, *J* =
424 2.9 Hz, H-12), 5.12 (s, 2H, H-31), 3.70 (d, 1H, *J* = 10.3 Hz, H-23_a), 3.61 (brt, 1H, *J* = 8.4
425 Hz, H-3), 3.39 (d, 1H, *J* = 10.3 Hz, H-23_b), 2.78 (dd, 1H, *J* = 13.8, 3.8 Hz, H-18), 1.07 (s,
426 3H, C), 0.89 (s, 3H, C), 0.87 (s, 3H, CH_3), 0.86 (s, 6H, 2xCH_3), 0.48 (s, 3H, CH_3); ^{13}C
427 NMR (75 MHz, $CDCl_3$): δ = 177.85 (C-28), 162.99 (d, *J* = 246.8 Hz, C-38), 144.26 (C-13),
428 143.65 (C-32), 130.38 (d, *J* = 3.0 Hz, C-35), 130.11 (d, *J* = 8.1 Hz, C-36, C-36'), 124.42
429 (C-12), 122.47 (C-33), 116.28 (d, *J* = 21.7 Hz, C-37, C-37'), 76.85 (C-3), 72.12 (C-23),
430 57.50 (C-31), 53.20 (C-34), 49.85 (C-9), 47.61 (C-17), 46.81 (C-5), 45.93 (C-19), 41.88
431 (C-4), 41.82 (C-14), 41.36 (C-18), 39.36 (C-8), 38.20 (C-1), 36.98 (C-10), 33.91 (C-21),
432 33.14 (C-29), 32.54 (C-7), 32.41 (C-22), 30.70 (C-20), 27.70 (C-15), 26.77 (C-27), 25.91
433 (C-2), 23.67 (C-30), 23.43 (C-11), 23.06 (C-16), 18.56 (C-6), 16.81 (C-26), 15.81 (C-25),
434 11.55 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{56}FN_3O_4]^+$: 662.4333, found:
435 662.4327; CHN calcd.: C, 72.58; H, 8.53; N, 6.35; found: C, 72.40; H, 8.68; N, 6.09.

436 *4.5.13 (p-Nitrobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-*
437 *oate (**14**).*

White solid; yield: 50 mg, 44%; m.p. 183.6-184.8 ^{o}C; R_f = 0.43 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3404, 3152, 3086, 1720, 1526, 1162, 1054, 1038 802 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, 2H, , J = 8.4 Hz,H-37, H-37'), 7.58 (s, 1H, H-33), 7.39 (d, 2H, J = 8.3 Hz, H-36, H-36'), 5.61 (t, 2H, J = 16.6 Hz, H-34), 5.23 (brs, 1H, H-12), 5.16 (s, 2H, H-31), 3.70 (d, 1H, J = 10.3 Hz, H-23$_a$), 3.61 (brt, 1H, J = 8.1 Hz, H-3), 3.40 (d, 1H, J = 10.3 Hz, H-23$_b$), 2.79 (brdd, 1H, J = 13.4 Hz, H-18), 1.08 (s, 3H, CH_3), 0.87 (s, 12H, 4xCH_3), 0.50 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.92 (C-28), 148.23 (C-38), 144.26 (C-13), 143.65 (C-32), 141.59 (C-35), 128.72 (C-36, C-36'), 124.22 (C-37, C-37'), 124.42 (C-12), 122.47 (C-33), 76.85 (C-3), 72.12 (C-23), 57.50 (C-31), 53.20 (C-34), 49.81 (C-9), 47.61 (C-17), 46.86 (C-5), 45.93 (C-19), 41.89 (C-4), 41.85 (C-14), 41.39 (C-18), 39.39 (C-8), 38.20 (C-1), 36.98 (C-10), 33.92 (C-21), 33.16 (C-29), 32.57 (C-7), 32.46 (C-22), 30.76 (C-20), 27.72 (C-15), 26.81 (C-27), 25.91 (C-2), 23.67 (C-30), 23.45 (C-11), 23.10 (C-16), 18.56 (C-6), 16.88 (C-26), 15.82 (C-25), 11.53 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{56}N_4O_6]^+$: 689.4278, found: 689.4269; CHN calcd.: C, 69.74; H, 8.19; N, 8.13; found: C, 69.51; H, 8.35; N, 8.00.

*4.5.14 (m-Nitrobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-oate (**15**).*

White solid; yield: 60 mg, 52%; m.p. 152.7-153.9 ^{o}C; R_f = 0.43 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3404, 3156, 3092, 1718, 1534, 1174, 1158, 1048, 728 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (m, 1H, H-38), 8.13 (brs, 1H, H-36), 7.59 (brs, 1H, H-33), 7.56 (m, 2H, H-39, H-40), 5.63 (d, 1H, J = 15.3 Hz, H-34$_a$), 5.57 (d, 1H, J = 15.3 Hz, H-34$_b$), 5.22 (t, 1H, J = 3.0 Hz, H-12), 5.15 (s, 2H, H-31), 3.69 (d, 1H, J = 10.3 Hz, H-23$_a$),

3.60 (brt, 1H, *J* = 8.6 Hz, H-3), 3.39 (d, 1H, *J* = 10.3 Hz, H-23$_b$), 2.79 (dd, 1H, *J* = 13.6, 3.7 Hz, H-18), 1.08 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.86 (s, 9H, 3xCH_3), 0.50 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.89 (C-28), 148.67 (C-37), 144.19 (C-13), 142.63 (C-32), 136.66 (C-35), 133.96 (C-40), 130.42 (C-39), 124.31 (C-12), 123.94 (C-36), 122.95 (C-38), 122.46 (C-33), 76.86 (C-3), 72.10 (C-23), 57.49 (C-31), 53.20 (C-34), 49.83 (C-9), 47.59 (C-17), 46.83 (C-5), 45.91 (C-19), 41.87 (C-4), 41.82 (C-14), 41.38 (C-18), 39.37 (C-8), 38.19 (C-1), 36.97 (C-10), 33.89 (C-21), 33.13 (C-29), 32.55 (C-7), 32.42 (C-22), 30.74 (C-20), 27.70 (C-15), 26.77 (C-27), 25.91 (C-2), 23.66 (C-30), 23.42 (C-11), 23.07 (C-16), 18.56 (C-6), 16.85 (C-26), 15.80 (C-25), 11.56 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{56}N_4O_6]^+$: 689.4278, found: 689.4269; CHN calcd.: C, 69.74; H, 8.19; N, 8.13; found: C, 69.54; H, 8.33; N, 8.04.

*4.5.15 (o-Nitrobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-oate (**16**).*

White solid; yield: 87 mg, 76%; m.p. 123.8-125.3 ^oC; R_f = 0.43 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3046, 3158, 3060, 1722, 1530, 1160, 1048, 1004, 728 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (dd, 1H, *J* = 7.9, 1.3 Hz,H-37), 7.71 (brs, 1H, H-33), 7.60 (td, 2H, *J* = 7.4, 1.3 Hz, H-38), 7.53 (td, 2H, *J* = 7.4, 1.3 Hz, H-39);7.07 (dd, 1H, *J* = 7.6, 1.3 Hz, H-40), 5.90 (s, 2H, H-34), 5.24 (t, 1H, *J* = 3.1 Hz, H-12), 5.17 (s, 2H, H-31), 3.70 (d, 1H, *J* = 10.3 Hz, H-23$_a$), 3.61 (brt, 1H, *J* = 8.2 Hz, H-3), 3.40 (d, 1H, *J* = 10.3 Hz, H-23$_b$), 2.81 (dd, 1H, *J* = 13.8, 3.8 Hz, H-18), 1.09 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.87 (s, 9H, 3x CH_3), 0.55 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.77 (C-28), 147.59 (C-36), 143.90 (C-13), 143.64 (C-32), 134.43 (C-35), 130.53 (C-39), 130.51 (C-40), 129.88 (C-38),

125.55 (C-37), 125.04 (C-12), 122.52 (C-33), 76.89 (C-3), 72.13 (C-23), 57.55 (C-31), 50.94 (C-34), 49.86 (C-9), 47.64 (C-17), 46.84 (C-5), 45.92 (C-19), 41.89 (C-4), 41.83 (C-14), 41.38 (C-18), 39.40 (C-8), 38.21 (C-1), 37.00 (C-10), 33.92 (C-21), 33.16 (C-29), 32.55 (C-7), 32.44 (C-22), 30.77 (C-20), 27.73 (C-15), 26.80 (C-27), 25.94 (C-2), 23.71 (C-30), 23.45 (C-11), 23.07 (C-16), 18.59 (C-6), 16.92 (C-26), 15.81 (C-25), 11.56 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{56}N_4O_6]^+$: 689.4278,found: 689.4270; CHN calcd.: C, 69.74; H, 8.19; N, 8.13; found: C, 69.63; H, 8.40; N, 8.02.

4.15.16 (Benzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-amide ***(17)****.*

White solid; yield: 97mg, 90%; m.p. 124.8-126.3 ^oC; R_f = 0.42 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3402, 3150, 3066,1722, 1636, 1520, 1048, 724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72 (s, 1H, H-33), 7.33(brs, 3H), 7.26 (brs, 2H), 6.61 (t, 1H, *J* = 4.7 Hz, N-H), 5.49 (d, 1H, *J* = 14.8 Hz, H-34_a), 5.42 (d, 1H, *J* = 14.8 Hz, H-34_b), 5.35 (brs, 1H, H-12), 4.45 (dd, 1H, *J* =15.0, 5.2 Hz, H-31_a), 4.31 (dd, 1H, *J* =15.0, 5.2 Hz, H-31_b), 3.68 (d, 1H, *J* = 10.3 Hz, H-23_a), 3.61 (brt, 1H, *J* = 7.9 Hz, H-3), 3.38 (d, 1H, *J* = 10.3 Hz, H-23_b), 2.51 (brdd, 1H, *J* = 11.1 Hz, H-18), 1.10 (s, 3H, CH_3), 0.87 (s, 6H, 2xCH_3), 0.86 (s, 6H, 2xCH_3), 0.44 (s, H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.56 (C-28), 145.17 (C-13), 144.28 (C-32), 134.60 (C-35), 129.19 (C-37), 129.19 (C-37'), 128.89 (C-38), 128.19 (C-36'), 128.19 (C-36), 123.27 (C-12), 122.55 (C-33), 76.63 (C-3), 71.84 (C-23), 54.28 (C-34), 49.68 (C-9), 47.59 (C-17), 46.72 (C-5), 46.32 (C-19), 42.08 (C-4), 42.06 (C-14), 41.89 (C-18), 39.37 (C-8), 38.26 (C-1), 36.91 (C-10), 35.14 (C-31), 34.19 (C-21), 33.08 (C-29), 32.55 (C-7), 32.20 (C-22), 30.80 (C-20), 27.30 (C-15), 26.69 (C-27), 25.85 (C-2), 23.92

(C-30), 23.68 (C-11), 23.52 (C-16), 18.52 (C-6), 16.61 (C-26), 15.87 (C-25), 11.62 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{58}N_4O_3]^+$: 643.4587, found: 643.4578; CHN calcd.: C, 74.73; H, 9.09; N, 8.71; found: C, 74.51; H, 9.23; N, 8.55.

*4.5.17 (o-Bromobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-amide (**18**).*

White solid; yield: 102mg, 85%; m.p. 128.3-130.2 ^oC; R_f = 0.42 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3386, 3150, 3070,1720, 1636, 1522, 1046, 1030, 748, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.58 (brs, 1H, H-37), 7.56 (s, 1H, H-33), 7.22 (m, H-38, H-39, H-40), 6.62 (t, 1H, *J* = 6.3 Hz, N-H), 5.59 (s, 2H, H-34), 5.36 (brs, 1H, H-12), 4.47 (dd, 1H, *J* =14.8, 5.1 Hz, H-31_a), 4.32 (dd, 1H, *J* =14.8, 5.1 Hz, H-31_b), 3.68 (d, 1H, *J* = 10.0 Hz, H-23_a), 3.60 (brt, 1H, *J* = 7.9 Hz, H-3), 3.37 (d, 1H, *J* = 10.0 Hz, H-23_b), 2.51 (brdd, 1H, *J* = 11.2 Hz, H-18), 1.10 (s, 3H, CH_3), 0.86 (s, 6H, 2xCH_3), 0.85 (s, 6H, 2xCH_3), 0.46 (s, H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.55 (C-28), 145.05 (C-13), 144.29 (C-32), 134.10 (C-35), 133.36 (C-37), 130.56 (C-40), 130.56 (C-39), 128.25 (C-38), 123.68 (C-36), 123.26 (C-12), 122.97 (C-33), 76.60 (C-3), 71.80 (C-23), 53.93 (C-34), 49.67 (C-9), 47.58 (C-17), 46.71 (C-5), 46.32 (C-19), 42.06 (C-4), 42.06 (C-14), 41.88 (C-18), 39.37 (C-8), 38.25 (C-1), 36.90 (C-10), 35.12 (C-31), 34.20 (C-21), 33.08 (C-29), 32.56 (C-7), 32.20 (C-22), 30.79 (C-20), 27.32 (C-15), 26.66 (C-27), 25.85 (C-2), 23.91 (C-30), 23.68 (C-11), 23.53 (C-16), 18.53 (C-6), 16.62 (C-26), 15.87 (C-25), 11.63 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{57}BrN_4O_3]^+$: 721.3672, found: 721.3679; CHN calcd.: C, 66.56; H, 7.96; N, 7.76; found: C, 66.39; H, 8.11; N, 7.59.

*4.5.18 (m-Bromobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-amide (**19**).*

White solid; yield: 108mg, 90%; m.p. 123.6-125.2 ^{o}C; R_f = 0.44 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3394, 3148, 3064, 1730, 1636, 1519, 1240, 1048, 770, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (s, H, H-33), 7.46 (d, 1H, *J* = 7.3 Hz, H-38), 7.40 (s, 1H, H-36), 7.22 (m, 2H, H-39, H-40), 6.61 (t, 1H, *J* = 4.7 Hz, N-H), 5.47 (d, 1H, *J* = 15.7 Hz, H-34_a), 5.39 (d, 1H, *J* = 15.7 Hz, H-34_b), 5.36 (brs, 1H, H-12), 4.46 (dd, 1H, *J* =15, 5.1 Hz, H-31_a), 4.33 (dd, 1H, *J* =15, 5.1 Hz, H-31_b), 3.69 (d, 1H, *J* = 10.1 Hz, H-23_a), 3.61 (brt, 1H, *J* = 8.0 Hz, H-3), 3.39 (d, 1H, *J* = 10.2 Hz, H-23_b), 2.52 (brdd, 1H, *J* = 11.6 Hz, H-18), 1.11 (s, 3H, CH_3), 0.86 (s, 12H, 4xCH_3), 0.44 (s, H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.65 (C-28), 145.44 (C-13), 144.31 (C-32), 136.83 (C-35), 132.06 (C-38), 131.15 (C-36), 130.72 (C-39), 126.71 (C-40), 123.20 (C-37), 123.27 (C-12), 122.72 (C-33), 76.73 (C-3), 71.93 (C-23), 53.47 (C-34), 49.71 (C-9), 47.59 (C-17), 46.73 (C-5), 46.34 (C-19), 42.12 (C-4), 42.08 (C-14), 41.90 (C-18), 39.38 (C-8), 38.25 (C-1), 36.91 (C-10), 35.16 (C-31), 34.20 (C-21), 33.09 (C-29), 32.57 (C-7), 32.24 (C-22), 30.81 (C-20), 27.32 (C-15), 26.74 (C-27), 25.86 (C-2), 23.96 (C-30), 23.69 (C-11), 23.53 (C-16), 18.56 (C-6), 16.63 (C-26), 15.87 (C-25), 11.61 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{57}BrN_4O_3]^+$: 721.3672, found: 721.3686; CHN calcd.: C, 66.56; H, 7.96; N, 7.76; found: C, 66.44; H, 8.14; N, 7.51.

*4.5.19 (p-Bromobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-amide (**20**).*

White solid; yield: 114mg, 95%; m.p. 143.6-145.2 ^{o}C; R_f = 0.42 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3414, 3150, 1636, 1048, 1012 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (s, 1H, H-33), 7.47 (d, 2H, *J* = 8.2 Hz, H-37, H-37'), 7.13 (d, 2H, *J* = 8.1 Hz, H-36, H-36'), 6.60 (t, 1H, *J* = 5.1 Hz, N-H), 5.45 (d, 1H, *J* = 14.8 Hz, H-34$_a$), 5.37 (d, 1H, *J* = 14.8 Hz, H-34$_b$), 5.34 (brs, 1H, H-12), 4.44 (dd, 1H, *J* =15.0, 5.3 Hz, H-31$_a$), 4.32 (dd, 1H, *J* =15.0, 5.3 Hz, H-31$_b$), 3.69 (d, 1H, *J* = 10.2 Hz, H-23$_a$), 3.61 (brt, 1H, *J* = 7.0 Hz, H-3), 3.38 (d, 1H, *J* = 10.2 Hz, H-23$_b$), 2.50 (brdd, 1H, *J* = 11.0 Hz, H-18), 1.10 (s, 3H, CH_3), 0.86 (s, 12H, 4xCH_3), 0.41 (s, H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.67 (C-28), 145.39 (C-13), 144.31 (C-32), 133.69 (C-35), 132.36 (C-37, C-37'), 129.82 (C-36, C-36'), 123.26 (C-12), 123.08 (C-38), 122.68 (C-33), 76.68 (C-3), 71.90 (C-23), 53.55 (C-34), 49.69 (C-9), 47.57 (C-17), 46.73 (C-5), 46.33 (C-19), 42.09 (C-4), 42.06 (C-14), 41.90 (C-18), 39.35 (C-8), 38.25 (C-1), 36.90 (C-10), 35.16 (C-31), 34.19 (C-21), 33.07 (C-29), 32.56 (C-7), 32.21 (C-22), 30.80 (C-20), 27.29 (C-15), 26.72 (C-27), 25.84 (C-2), 23.95 (C-30), 23.66 (C-11), 23.52 (C-16), 18.49 (C-6), 16.62 (C-26), 15.86 (C-25), 11.63 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{58}BrN_4O_3]^+$:721.3672, found: 721.3689; CHN calcd.: C, 66.56; H, 7.96; N, 7.76; found: C, 66.31; H, 8.10; N, 7.61.

*4.5.20 (2,6-Dichlorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-amide (**21**).*

White solid; yield: 89mg, 75%; m.p. 144.8-146.3 ^{o}C; R_f = 0.44 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3404, 3150, 3078, 1636, 1520, 1048, 764, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (s, 1H, H-33), 7.37 (d, 2H, *J* = 7.2 Hz, H-37, H-40), 7.29 (d, 1H, *J* = 7.9 Hz, H-38), 6.59 (t, 1H, *J* = 4.9 Hz, N-H), 5.79 (t, 2H, *J* = 15.6 Hz, H-34), 5.34 (brs,

1H, H-12), 4.45 (dd, 1H, *J* =15.0, 5.1 Hz, H-31$_a$), 4.31 (dd, 1H, *J* =15.0, 5.1 Hz, H-31$_b$), 3.67 (d, 1H, *J* = 10.3 Hz, H-23$_a$), 3.60 (brt, 1H, *J* = 7.9 Hz, H-3), 3.37 (d, 1H, *J* = 10.3 Hz, H-23$_b$), 2.51 (brdd, 1H, *J* = 11.5 Hz, H-18), 1.09 (s, 3H, CH_3), 0.86 (s, 6H, 2xCH_3), 0.85 (s, 6H, 2xCH_3), 0.42 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.43 (C-28), 144.65 (C-13), 144.23 (C-32), 136.88 (C-35), 131.20 (C-36), 130.04 (C-40), 128.99 (C-37), 128.99 (C-39), 128.99 (C-38), 123.24 (C-12), 122.23 (C-33), 76.61 (C-3), 71.81 (C-23), 49.10 (C-34), 49.68 (C-9), 47.58 (C-17), 46.70 (C-5), 46.30 (C-19), 42.02 (C-4), 42.02 (C-14), 41.87 (C-18), 39.35 (C-8), 38.25 (C-1), 36.89 (C-10), 35.02 (C-31), 34.20 (C-21), 33.08 (C-29), 32.57 (C-7), 32.21 (C-22), 30.79 (C-20), 27.29 (C-15), 26.66 (C-27), 25.85 (C-2), 23.88 (C-30), 23.66 (C-11), 23.51 (C-16), 18.52 (C-6), 16.52 (C-26), 15.85 (C-25), 11.63 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{56}Cl_2N_4O_3]^+$: 711.3808, found: 711.3799; CHN calcd.: C, 67.59; H, 7.80; N, 7.88; found: C, 67.41; H, 7.99; N, 7.67.

*4.5.21 (p-Chlorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-amide (**22**).*

White solid; yield: 92mg, 81%; m.p. 139.3-141 ^{o}C; R_f = 0.44 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3402, 3152, 3068, 1718, 1636, 1520, 1048, 1016, 732cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (s, H, H-33), 7.31 (d, 2H, *J* = 8.2 Hz, H-37, H-37'), 7.19 (d, 2H, *J* = 8.2 Hz, H-36, H-36'), 6.60 (t, 1H, *J* = 4.4 Hz, N-H), 5.47 (d, 1H, *J* = 14.9 Hz, H-34$_a$), 5.38 (d, 1H, *J* = 14.9 Hz, H-34$_b$), 5.35 (brs, 1H, H-12), 4.44 (dd, 1H, *J* =14.9, 5.2 Hz, H-31$_a$), 4.32 (dd, 1H, *J* =14.9, 5.2 Hz, H-31$_b$), 3.68 (d, 1H, *J* = 10.2 Hz, H-23$_a$), 3.60 (brt, 1H, *J* = 8.0 Hz, H-3), 3.38 (d, 1H, *J* = 10.2 Hz, H-23$_b$), 2.50 (brdd, 1H, *J* = 11.8 Hz, H-18), 1.10 (s, 3H, CH_3), 0.85 (s, 12H, 4xCH_3), 0.41 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ

590 = 178.68 (C-28), 145.38 (C-13), 144.29 (C-32), 134.95 (C-35), 133.17 (C-38), 129.54 (C-
591 36, C-36'), 129.39 (C-37, C-37'), 123.25 (C-12), 122.67 (C-33), 76.64 (C-3), 71.85 (C-23),
592 53.50 (C-34), 49.68 (C-9), 47.56 (C-17), 46.72 (C-5), 46.33 (C-19), 42.08 (C-4), 42.06 (C-
593 14), 41.88 (C-18), 39.35 (C-8), 38.24 (C-1), 36.89 (C-10), 35.15 (NH-C-31), 34.19 (C-21),
594 33.07 (C-29), 32.56 (C-7), 32.20 (C-22), 30.80 (C-20), 27.28 (C-15), 26.69 (C-27), 25.84
595 (C-2), 23.93 (C-30), 23.65 (C-11), 23.51 (C-16), 18.47 (C-6), 16.61 (C-26), 15.84 (C-25),
596 11.61 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{57}ClN_4O_3]^+$: 677.4197, found:
597 677.4191; CHN calcd.: C, 70.93; H, 8.48; N, 8.27; found: C, 70.19; H, 8.57; N, 8.03.

598 *4.5.22 (m-Chlorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-*
599 *amide (**23**).*

600 White solid; yield: 89mg, 78%; m.p. 143.4-144.8 ^oC; R_f = 0.46 (hexane/ethylacetate 1:1
601 v/v); IR (KBr): $\bar{\upsilon}$ = 3404, 3150, 3086, 1636, 1520, 1048, 772, 732 cm^{-1}; ^1H NMR (300
602 MHz, $CDCl_3$): δ = 7.52 (s, H, H-33), 7.26 (m, 3H, H-36, H-38, H-39), 7.13 (d, 1H, *J* = 6.7
603 Hz, H-40), 6.63 (t, 1H, *J* = 5.6 Hz, N-H), 5.47 (d, 1H, *J* = 15.1 Hz, H-34_a), 5.39 (d, 1H, *J* =
604 15.1 Hz, H-34_b), 5.36 (brs, 1H, H-12), 4.45 (dd, 1H, *J* =15.0, 5.1 Hz, H-31_a), 4.32 (dd, 1H,
605 *J* =15.0, 5.1 Hz, H-31_b), 3.68 (d, 1H, *J* = 10.3 Hz, H-23_a), 3.61 (brt, 1H, *J* = 7.5 Hz, H-3),
606 3.38 (d, 1H, *J* = 10.3 Hz, H-23_b), 2.51 (brdd, 1H, *J* = 13.2 Hz, H-18), 1.10 (s, 3H, CH_3),
607 0.85 (s, 12H, 4xCH_3), 0.44 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.67 (C-28),
608 145.41 (C-13), 144.28 (C-32), 136.57 (C-35), 135.11 (C-37), 130.46 (C-39), 129.11 (C-36),
609 128.23 (C-38), 126.22 (C-40), 123.27 (C-12), 122.75 (C-33), 76.65 (C-3), 71.85 (C-23),
610 53.53 (C-34), 49.69 (C-9), 47.57 (C-17), 46.71 (C-5), 46.33 (C-19), 42.09 (C-4), 42.06 (C-
611 14), 41.88 (C-18), 39.37 (C-8), 38.24 (C-1), 36.89 (C-10), 35.14 (C-31), 34.18 (C-21),

33.07 (C-29), 32.55 (C-7), 32.22 (C-22), 30.79 (C-20), 27.29 (C-15), 26.68 (C-27), 25.84 (C-2), 23.92 (C-30), 23.67 (C-11), 23.51 (C-16), 18.52 (C-6), 16.61 (C-26), 15.84 (C-25), 11.61 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{57}ClN_4O_3]^+$: 677.4197, found: 677.4191; CHN calcd.: C, 70.93; H, 8.48; N, 8.27; found: C, 70.76; H, 8.51; N, 8.19.

*4.5.23 (o-Chlorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-amide (**24**).*

White solid; yield: 90mg, 79%; m.p. 133-134.1 ^oC; R_f = 0.44 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3400, 3150, 3072, 1722, 1636, 1520, 1048, 752, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 1H, H-33), 7.41 (d, 1H, H-37), 7.25 (m, 3H, H-38, H-39, H-40), 6.59 (t, 1H, J = 4.3 Hz, N-H), 5.60 (t, 2H, J = 15.2 Hz, H-34), 5.36 (brs, 1H, H-12), 4.48 (dd, 1H, J =15.0, 5.0 Hz, H-31_a), 4.34 (dd, 1H, J =15.0, 5.0 Hz, H-31_b), 3.70 (d, 1H, J = 10.3 Hz, H-23_a), 3.61 (brt, 1H, J = 7.7 Hz, H-3), 3.39 (d, 1H, J = 10.3 Hz, H-23_b), 2.52 (brdd, 1H, J = 11.8 Hz, H-18), 1.11 (s, 3H, CH_3), 0.87 (s, 12H, 4xCH_3), 0.47 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.54 (C-28), 145.10 (C-13), 144.34 (C-32), 133.72 (C-35), 132.44 (C-36), 130.58 (C-40), 130.41 (C-37), 130.09 (C-38), 127.65 (C-39), 123.27 (C-12), 122.91 (C-33), 76.63 (C-3), 71.98 (C-23), 51.55 (C-34), 49.72 (C-9), 47.62 (C-17), 46.75 (C-5), 46.35 (C-19), 42.12 (C-4), 42.08 (C-14), 41.92 (C-18), 39.40 (C-8), 38.26 (C-1), 36.93 (C-10), 35.15 (C-31), 34.22 (C-21), 33.16 (C-29), 32.57 (C-7), 32.22 (C-22), 30.82 (C-20), 27.33 (C-15), 26.78 (C-27), 25.87 (C-2), 23.96 (C-30), 23.69 (C-11), 23.55 (C-16), 18.57 (C-6), 16.63 (C-26), 15.87 (C-25), 11.58 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{57}ClN_4O_3]^+$: 677.4197, found: 677.4190; CHN calcd.: C, 70.93; H, 8.48; N, 8.27; found: C, 70.77; H, 8.63; N, 8.19.

*4.5.24 (2,4-Difluorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-amide (**25**).*

White solid; yield: 95mg, 84%; m.p. 119.3-120.8 ^{o}C; R_f = 0.44 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3404, 3150, 3080, 1636, 1508, 1276, 1048, 1004, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 1H, H-33),7.27 (m, 1H, H-40), 6.84 (m, 2H, H-37, H-39), 6.61 (t, 1H, *J* = 4.5 Hz, N-H), 5.47 (t, 2H, *J* = 15.4 Hz, H-34), 5.34 (brs, 1H, H-12), 4.44 (dd, 1H, *J* =15.0, 5.1 Hz, H-31_a), 4.32 (dd, 1H, *J* =15.0, 5.1 Hz, H-31_b), 3.67 (d, 1H, *J* = 10.3 Hz, H-23_a), 3.60 (brt, 1H, *J* = 8.0 Hz, H-3), 3.37 (d, 1H, *J* = 10.3 Hz, H-23_b), 2.50 (brdd, 1H, *J* = 11.5 Hz, H-18), 1.09 (s, 3H, CH_3), 0.85 (s, 12H, 4xCH_3), 0.40 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.63 (C-28), 163.42 (dd, *J* = 249.9, 11.6 Hz, C-38), 160.85 (dd, *J* = 249.3, 11.8 Hz, C-36), 145.28 (C-13), 144.26 (C-32), 131.80 (dd, *J* = 9.8, 4.6 Hz, C-40), 123.26 (C-12), 122.74 (C-33), 118.05 (dd, *J* = 14.6, 3.7 Hz, C-35), 112.20 (dd, *J* = 21.5, 3.8 Hz, C-39), 104.51 (t, *J* = 25.2 Hz, C-37), 76.57 (C-3), 71.76 (C-23), 49.65 (C-9), 47.56 (C-17), 47.22 (d, *J* = 3.5 Hz, C-34), 46.70 (C-5), 46.33 (C-19), 42.07 (C-4), 42.04 (C-14), 41.86 (C-18), 39.34 (C-8), 38.24 (C-1), 36.88 (C-10), 35.07 (C-31), 34.18 (C-21), 33.06 (C-29), 32.56 (C-7), 32.20 (C-22), 30.78 (C-20), 27.27 (C-15), 26.64 (C-27), 25.83 (C-2), 23.91 (C-30), 23.64 (C-11), 23.50 (C-16), 18.46 (C-6), 16.51 (C-26), 15.81 (C-25), 11.60 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{56}F_2N_4O_3]^+$: 679.4399, found: 679.4390; CHN calcd.: C, 70.77; H, 8.31; N, 8.25; found: C, 70.51; H, 8.52; N, 8.13.

*4.5.25 (o-Fluorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-amide (**26**).*

White solid; yield: 78mg, 70%; m.p. 122.3-123.8 ^{o}C; R_f = 0.46 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3404, 3150, 3052, 1636, 1522, 1236, 1048, 1004, 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (s, H, H-33), 7.33 (m, 1H, H-40), 7.25 (m, 1H, H-38), 7.10 (m, 2H, H-37, H-39), 6.61 (t, 1H, *J* = 3.9 Hz, N-H), 5.52 (t, 2H, *J* = 15.4 Hz, H-34), 5.35 (brs, 1H, H-12), 4.45 (dd, 1H, *J* =15.0, 5.3 Hz, H-31$_a$), 4.33 (dd, 1H, *J* =15.0, 5.3 Hz, H-31$_b$), 3.68 (d, 1H, *J* = 10.3 Hz, H-23$_a$), 3.61 (brt, 1H, *J* = 8.0 Hz, H-3), 3.38 (d, 1H, *J* =10.3 Hz, H-23$_b$), 2.51 (brdd, 1H, *J* = 12.1 Hz, H-18), 1.10 (s, 3H, CH_3), 0.86 (s, 12H, 4xCH_3), 0.43 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.54 (C-28), 160.66 (d, *J* = 246.7 Hz, C-36), 145.15 (C-13), 144.27 (C-32), 131.06 (d, *J* = 8.1 Hz, C-40), 130.71 (d, *J* = 3.2 Hz, C-38), 124.88 (d, *J* = 3.7 Hz, C-35), 123.27 (C-12), 122.71 (C-33), 121.89 (d, *J* = 14.5 Hz, C-39), 115.97 (d, *J* = 20.9 Hz, C-37), 76.64 (C-3), 71.84 (C-23), 49.69 (C-9), 47.58 (C-17), 47.80 (d, *J* = 4.2 Hz, C-34), 46.72 (C-5), 46.33 (C-19), 42.08 (C-4), 42.05 (C-14), 41.88 (C-18), 39.37 (C-8), 38.25 (C-1), 36.90 (C-10), 35.08 (C-31), 34.20 (C-21), 33.08 (C-29), 32.55 (C-7), 32.20 (C-22), 30.80 (C-20), 27.30 (C-15), 26.68 (C-27), 25.85 (C-2), 23.91 (C-30), 23.67 (C-11), 23.52 (C-16), 18.52 (C-6), 16.54 (C-26), 15.84 (C-25), 11.62 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{57}FN_4O_3]^+$: 661.4493, found: 661.4488; CHN calcd.: C, 72.69; H, 8.69; N, 8.48; found: C, 72.48; H, 8.85; N, 8.22.

*4.5.26 (2,6-Difluorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-amide (**27**).*

White solid; yield: 113 mg, 97%; m.p. 139.8-140.9 ^{o}C; R_f = 0.44 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3404, 3150, 3094, 1628, 1522, 1238, 1048, 1032, 802, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 1H, H-33), 7.34 (m, 1H, H-38), 6.93 (m, 2H, H-37,

H-39), 6.63 (t, 1H, *J* = 4.7 Hz, N-H), 5.58 (d, 1H, *J* = 14.6 Hz, H-34_a), 5.51 (d, 1H, *J* = 14.6 Hz, H-34_b), 5.33 (brs, 1H, H-12), 4.42 (dd, 1H, *J* =14.9, 5.4 Hz, H-31_a), 4.31 (dd, 1H, *J* =14.9, 5.4 Hz, H-31_b), 3.66 (d, 1H, *J* = 10.1 Hz, H-23_a), 3.59 (brt, 1H, *J* = 7.7 Hz, H-3), 3.37 (d, 1H, *J* = 10.1 Hz, H-23_b), 2.50 (brdd, 1H, *J* = 11.8 Hz, H-18), 1.08 (s, 3H, CH_3), 0.84 (s, 12H, 4xCH_3), 0.39 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.52 (C-28), 161.42 (dd, *J* = 250.0, 6.8 Hz, C-36, C-40), 144.96 (C-13), 144.16 (C-32), 131.53 (t, *J* = 10.2 Hz, C-38), 123.26 (C-12), 122.59 (C-33), 111.89 (m, C-37, C-39), 110.73 (t, *J* = 18.9 Hz, C-35), 76.52 (C-3), 71.68 (C-23), 49.64 (C-9), 47.54 (C-17), 46.67 (C-5), 46.29 (C-19), 42.00 (C-4), 42.00 (C-14), 41.83 (C-18), 41.41 (t, *J* = 3.9Hz, C-34), 39.31 (C-8), 38.23 (C-1), 36.85 (C-10), 34.94 (C-31), 34.17 (C-21), 33.06 (C-29), 32.54 (C-7), 32.17 (C-22), 30.76 (C-20), 27.25 (C-15), 26.57 (C-27), 25.82 (C-2), 23.85 (C-30), 23.63 (C-11), 23.47 (C-16), 18.46 (C-6), 16.39 (C-26), 15.77 (C-25), 11.64 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{56}F_2N_4O_3]^+$:679.4391, found: 678.8946; CHN calcd.: C, 70.77; H, 8.31; N, 8.25; found: C, 70.61; H, 8.54; N, 8.01.

*4.5.27 (p-Fluorobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-amide (**28**).*

whitesolid; yield: 77 mg, 70%; m.p. 139.3-140.9 ^{o}C; R_f = 0.45 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3404, 3150, 3074, 1636, 1512, 1226, 1048, 1004, 776, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, H, H-33), 7.25 (m, 2H, H-36, H-36'), 7.02 (m, 2H, H-37, H-37'), 6.60 (t, 1H, *J* = 5.4 Hz, N-H), 5.47 (d, 1H, *J* = 14.8 Hz, H-34_a), 5.39 (d, 1H, *J* = 14.8 Hz, H-34_b), 5.35 (brs, 1H, H-12), 4.44 (dd, 1H, *J* =15.0, 5.4 Hz, H-31_a), 4.32 (dd, 1H, *J* =15.0, 5.4 Hz, H-31_b), 3.69 (d, 1H, *J* = 10.3 Hz, H-23_a), 3.61 (brt, 1H, *J* = 7.3 Hz, H-

3), 3.38 (d, 1H, J = 10.3 Hz, H-23$_b$), 2.51 (dd, 1H, J = 12.6, 3.0 Hz, H-18), 1.10 (s, 3H, CH_3), 0.86 (s, 9H, 3x CH_3), 0.85 (s, 3H, CH_3), 0.41 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.64 (C-28), 160.95 (d, J = 246.6 Hz, C-38), 145.34 (C-13), 144.29 (C-32), 130.55 (d, J = 3.3 Hz, C-35), 130.11 (d, J = 8.4 Hz, C-36, C-36'), 123.26 (C-12), 122.58 (C-33), 116.20 (d, J = 21.6 Hz, C-37, C-37'), 76.65 (C-3), 71.87 (C-23), 53.51 (C-34), 49.68 (C-9), 47.57 (C-17), 46.72 (C-5), 46.34 (C-19), 42.08 (C-4), 42.06 (C-14), 41.89 (C-18), 39.36 (C-8), 38.25 (C-1), 36.90 (C-10), 35.14 (C-31), 34.19 (C-21), 33.07 (C-29), 32.57 (C-7), 32.21 (C-22), 30.80 (C-20), 27.29 (C-15), 26.70 (C-27), 25.84 (C-2), 23.94 (C-30), 23.65 (C-11), 23.52 (C-16), 18.48 (C-6), 16.59 (C-26), 15.85 (C-25), 11.59 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{57}FN_4O_3]^+$: 661.4493, found: 661.4490; CHN calcd.: C, 72.69; H, 8.69; N, 8.48; found: C, 72.51; H, 8.75; N, 8.22.

*4.5.28 (p-Nitrobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-amide (**29**).*

White solid; yield: 77 mg, 66%; m.p. 158.4-159.7 ^{o}C; R_f = 0.43 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3404, 3150, 3080, 1636, 1524, 1048, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, 2H,J = 8.6 Hz, H-37, H-37'), 7.60 (s, 1H, H-33), 7.40 (d, 2H, J = 8.5 Hz, H-36, H-36'), 6.61 (t, 1H, J = 4.8 Hz, N-H), 5.62 (d, 1H, J = 15.3 Hz, H-34$_a$), 5.54 (d, 1H, J = 15.3 Hz, H-34$_b$), 5.36 (brs, 1H, H-12), 4.46 (dd, 1H, J =15.0, 5.4 Hz, H-31$_a$), 4.34 (dd, 1H, J =15.0, 5.4 Hz, H-31$_b$), 3.69 (d, 1H, J = 10.3 Hz, H-23$_a$), 3.61 (brt, 1H, J = 8.3 Hz, H-3), 3.38 (d, 1H, J = 10.3 Hz, H-23$_b$), 2.51 (brdd, 1H, J = 12.2 Hz, H-18), 1.10 (s, 3H, CH_3), 0.85 (s, 12H, 4x CH_3), 0.43 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.82 (C-28), 148.73 (C-38), 145.77 (C-13), 144.34 (C-32), 141.74 (C-35), 128.80 (C-36,

C-36'), 124.38 (C-37, C-37'), 123.28 (C-12), 122.19 (C-33), 76.68 (C-3), 71.93 (C-23), 53.19 (C-34), 49.66 (C-9), 47.55 (C-17), 46.73 (C-5), 46.36 (C-19), 42.08 (C-4), 42.08 (C-14), 41.83 (C-18), 39.36 (C-8), 38.24 (C-1), 36.90 (C-10), 35.19 (C-31), 34.19 (C-21), 33.06 (C-29), 32.58 (C-7), 32.23 (C-22), 30.80 (C-20), 27.28 (C-15), 26.71 (C-27), 25.84 (C-2), 23.99 (C-30), 23.64 (C-11), 23.53 (C-16), 18.47 (C-6), 16.68 (C-26), 15.86 (C-25), 11.56 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{57}N_5O_5]^+$: 688.4438, found: 688.4430; CHN calcd.: C, 69.84; H, 8.35; N, 10.18; found: C, 69.79; H, 8.49; N, 10.02.

*4.5.29 (m-Nitrobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxyolean-12-en-28-amide (**30**).*

White solid; yield: 91 mg, 79%; m.p. 149.3-150.8 ^oC; R_f = 0.43 (hexane/ethylacetate 1:1 v/v); IR (KBr): $\bar{\upsilon}$ = 3404, 3140, 3092, 1636, 1532, 1048, 722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.20 (dt, 1H, *J* = 7.7, 1.7 Hz, H-38), 8.14 (brs, 1H, H-36), 7.60 (brs, 1H, H-33), 7.56 (m, 2H, H-39, H-40), 6.63 (t, 1H, *J* = 5.4 Hz, N-H), 5.61 (d, 1H, *J* = 15.2 Hz, H-34_a), 5.55 (d, 1H, *J* = 15.2 Hz, H-34_b), 5.36 (brs, 1H, H-12), 4.47 (dd, 1H, *J* =15.0, 5.4 Hz, H-31_a), 4.33 (dd, 1H, *J* =15.0, 5.4 Hz, H-31_b), 3.68 (d, 1H, *J* = 10.3 Hz, H-23_a), 3.60 (brt, 1H, *J* = 8.4 Hz, H-3), 3.38 (d, 1H, *J* = 10.3 Hz, H-23_b), 2.51 (dd, 1H, *J* =12.3, 2.6 Hz, H-18), 1.10 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.85 (s, 9H, 3xCH_3), 0.44 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.76 (C-28), 148.65 (C-37), 145.71 (C-13), 144.30 (C-32), 136.79 (C-35), 134.01 (C-40), 130.33 (C-39), 123.87 (C-36), 123.26 (C-12), 123.02 (C-38), 123.02 (C-33), 76.67 (C-3), 71.89 (C-23), 53.18 (C-34), 49.67 (C-9), 47.55 (C-17), 46.70 (C-5), 46.34 (C-19), 42.08 (C-4), 42.06 (C-14), 41.87 (C-18), 39.37 (C-8), 38.23 (C-1), 36.90 (C-10), 35.14 (C-31), 34.17 (C-21), 33.06 (C-29), 32.57 (C-7), 32.23 (C-22), 30.79 (C-20),

744 27.29 (C-15), 26.69 (C-27), 25.84 (C-2), 23.94 (C-30), 23.64 (C-11), 23.51 (C-16), 18.48
745 (C-6), 16.65 (C-26), 15.82 (C-25), 11.58 (C-24); HRMS (ESI TOF-MS) $[M+H]^+$calcd. for
746 $[C_{40}H_{57}N_5O_5]^+$: 688.4438, found: 688.4429; CHN calcd.: C, 69.84; H, 8.35; N, 10.18;
747 found: C, 69.84; H, 8.57; N, 10.07.

748 *4.5.30 (o-Nitrobenzyl)-1H-1,2,3-triazol-4-yl-methyl-(3β)3,23-dihydroxy-olean-12-en-28-*
749 *amide (**31**).*

750 White solid; yield: 87 mg, 76%; m.p. 145.6-147.2 ^oC; R_f = 0.43 (hexane/ethylacetate 1:1
751 v/v); IR (KBr): $\bar{\upsilon}$ = 3398, 3150, 3080, 1636, 1530, 1048, 728 cm^{-1}; ^1H NMR (300 MHz,
752 $CDCl_3$): δ = 8.13 (dd, 1H, *J* = 7.9, 1.3 Hz, H-37), 7.67 (brs, 1H, H-33), 7.58 (td, 1H, *J*
753 =7.4, 1.5 Hz, H-38), 7.52 (td, 1H, *J* =7.4, 1.5 Hz, H-37), 7.04 (dd, 1H, *J* = 7.7, 1.3 Hz, H-
754 36), 6.64 (t, 1H, *J* = 5.3 Hz, N-H), 5.88 (s, 2H, H-34), 5.37 (brs, 1H, H-12), 4.52 (dd, 1H, *J*
755 =15.0, 5.3 Hz, H-31_a), 4.34 (dd, 1H, *J* =15.0, 5.3 Hz, H-31_b), 3.68 (d, 1H, *J* = 10.3 Hz, H-
756 23_a), 3.60 (brt, 1H, *J* = 8.1 Hz, H-3), 3.38 (d, 1H, *J* = 10.3 Hz, H-23_b), 2.53 (dd, 1H, *J*
757 =12.3, 2.3 Hz, H-18), 1.11 (s, 3H, CH_3), 0.87 (s, 6H, 2xCH_3), 0.86 (s, 3H, CH_3), 0.85 (s,
758 3H, CH_3), 0.52 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.64 (C-28), 147.58 (C-
759 36), 145.35 (C-13), 144.33 (C-32), 134.37 (C-35), 130.60 (C-39), 130.41 (C-40), 129.80
760 (C-38), 125.53 (C-37), 123.74 (C-12), 123.28 (C-33), 76.66 (C-3), 71.86 (C-23), 50.96 (C-
761 34), 49.69 (C-9), 47.59 (C-17), 46.71 (C-5), 46.35 (C-19), 42.09 (C-4), 42.06 (C-14), 41.88
762 (C-18), 39.40 (C-8), 38.24 (C-1), 36.91 (C-10), 35.15 (C-31), 34.19 (C-21), 33.08 (C-29),
763 32.57 (C-7), 32.22 (C-22), 30.80 (C-20), 27.33 (C-15), 26.68 (C-27), 25.87 (C-2), 23.92
764 (C-30), 23.68 (C-11), 23.54 (C-16), 18.52 (C-6), 16.70 (C-26), 15.84 (C-25), 11.60 (C-24);

765 HRMS (ESI TOF-MS) $[M+H]^+$calcd. for $[C_{40}H_{57}N_5O_5]^+$: 688.4438, found: 688.4434; CHN
766 calcd.: C, 69.84; H, 8.35; N, 10.18; found: C, 69.84; H, 8.55; N, 9.97.

767 *4.6 Cytotoxicity assay.*

768 The cytotoxicity of the compounds was evaluated using the sulforhodamine-B (SRB,
769 procured from Sigma-Aldrich, Wilwaukee, Wisconsin, USA) micro-culture colorimetric
770 assay. This assay is grounded on the proportional binding of a rhodamine dye to surface
771 membrane proteins, and there is a linear relationship between cell density and optical
772 density [32]. In short, exponentially growing cells were seeded into a 96-well plate on day
773 0 at the appropriate cell densities to prevent confluence of the cells during the period of
774 experiment. After 24 hours, the cells were treated with serial dilutions of the compounds (0-
775 30 µM) for 96 hours. The final concentration of DMSO never exceeded 0.5%, which was
776 non-toxic to the cells. The percentages of surviving cells relative to untreated controls were
777 determined 96 h after the beginning of drug exposure. After 96 hours of treatment, the
778 supernatant medium was discarded from the 96-well plates, and the cells were fixed with
779 10% TCA. For a thorough fixation, the plates were allowed to rest at 4 °C. After fixation,
780 the cells were washed in a strip washer. The washing was done four times with water using
781 alternate dispensing and aspiration procedures. The plates were dyed with 100 µL of 0.4%
782 SRB for about 20 min. After dying, the plates were washed with 1% acetic acid to remove
783 the excess of the dye and allowed to air-dry overnight. Tris base solution (100 µL, 10 mM)
784 was added to each well and absorbance was measured at λ = 570 nm (using a 96 well plate
785 reader, Tecan Spectra, Crailsheim, Germany). EC_{50} values were calculated from semi
786 logarithmic dose response curves by non-linear regression applying a two parametrical

787 Hill-slope equation. Values are given with a confidence interval CI = 95%; usually 7-13
788 dosage points were used

789 **ACKNOWLEDGEMENTS**

790 We are grateful to the following Brazilian agencies: Conselho Nacional de
791 Desenvolvimento Científico e Tecnológico (CNPq) for research fellowships (AJD, LCAB).
792 Fundação de Amparo à Pesquisa de Minas Gerais (FAPEMIG) for financial support and
793 Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for research
794 fellowship (DRH). We also thanks Dr. Carlos L. Zani and Dr. Markus Kohlhoff for HRMS
795 analysis (Centro de Pesquisas René Rachou (CPqRR) - FIOCRUZ MG-Brazil). The cell
796 lines were kindly provided by Dr. Thomas Müller (Dept. of Haematology/Oncology,
797 Martin-Luther University Halle-Wittenberg). Support by the “Science Campus- Plant based
798 bioeconomy” is gratefully acknowledged.

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Table 1.

Cytotoxicity for **He** and analogs **2-31**; cut-off in all experiments 30 μM except for parent **He** where the cut-off was 60 μM); employing human tumor cell lines and non-malignant mouse fibroblasts (NIH 3T3); betulinic acid (**BA**) was used as a standard.

EC_{50}*	Melanoma 518A2	Ovarian A2780	Lung A549	Colon HT29	Breast MCF7	Thyroid 8505C	NIH 3T3
He	>30	>30	>30	>30	>30	>30	>30
2	16.3	14.1	18.4	2.8	9.3	15.3	11.8
3	13.8	12.2	18.3	11.6	10.0	19.6	9.6
4	4.0	3.7	3.7	3.7	3.2	3.7	3.4
5	9.4	10.8	9.3	11.6	6.5	9.8	7.5
6	12.5	11.7	15.8	7.7	8.8	24.8	9.2
7	9.9	12.3	7.9	11.1	6.6	9.8	8.1
8	4.0	3.8	3.8	3.5	3.1	3.7	3.1
9	6.1	6.5	8.3	3.9	4.1	6.3	4.0
10	10.2	11.7	9.5	9.9	7.1	9.7	9.3
11	11.3	9.1	16.9	1.6	6.2	12.8	8.7
12	11.3	10.5	10.7	3.0	7.6	12.6	8.5
13	10.4	11.4	8.3	9.6	6.3	9.5	7.4
14	21.8	7.4	25.9	9.7	5.2	>30	5.6
15	4.1	3.6	3.7	3.5	3.2	3.6	3.1
16	17.5	10.8	14.9	7.1	9.1	18.5	11.8
17	17.3	13.7	12.2	9.5	9.5	>30	10.1
18	>30	11.9	>30	8.2	5.9	>30	6.8
19	>30	21.3	19.1	10.8	6.2	>30	8.2
20	10.9	12.2	27.5	16.3	4.5	>30	5.0
21	29.0	14.7	>30	5.8	6.4	>30	6.7
22	14.8	11.0	>30	14.0	6.0	>30	5.7
23	20.2	15.5	12.3	11.4	7.0	>30	6.7
24	20.1	11.1	>30	7.3	7.0	>30	7.2
25	12.3	11.2	10.4	7.9	6.9	18.1	7.8
26	13.1	11.1	10.2	6.3	7.4	22.7	7.7
27	12.9	10.3	25.9	5.2	7.7	15.8	8.3
28	9.5	10.5	26.8	7.8	9.2	25.2	7.5
29	>30	9.2	26.9	5.4	9.2	>30	8.1
30	>30	9.2	26.9	5.4	9.2	>30	8.1
31	>30	10.4	>30	6.6	10.1	>30	7.6
BA	9.4	8.8	17.1	14.4	10.2	--	16.1

*EC_{50} values in μM from SRB assays after 96 h of treatment; the values are averaged from at least three independent experiments performed each in triplicate; confidence interval CI = 95%;(individual positive (upper value) and negative (lower value) errors are given in the Table S1 of supplementary part

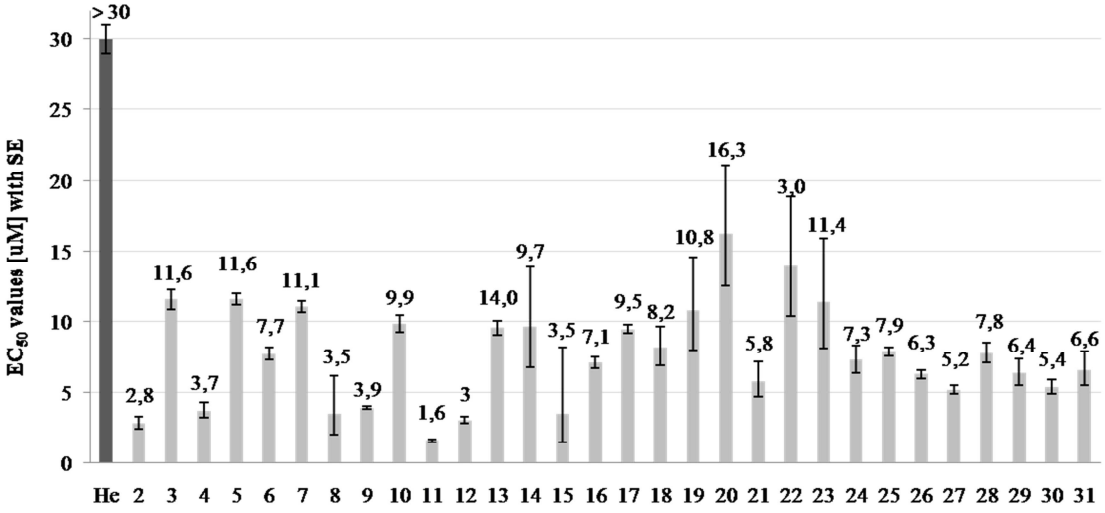


Figure 1. Cytotoxicity for **He** and derivatives compounds (**2-31**) using the human colon adenocarcinoma cancer cell line HT29.

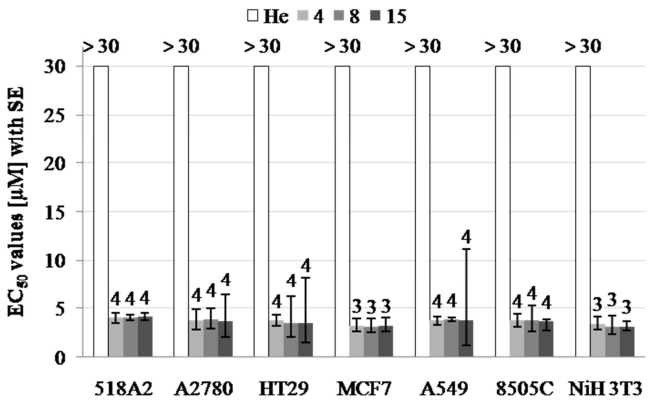
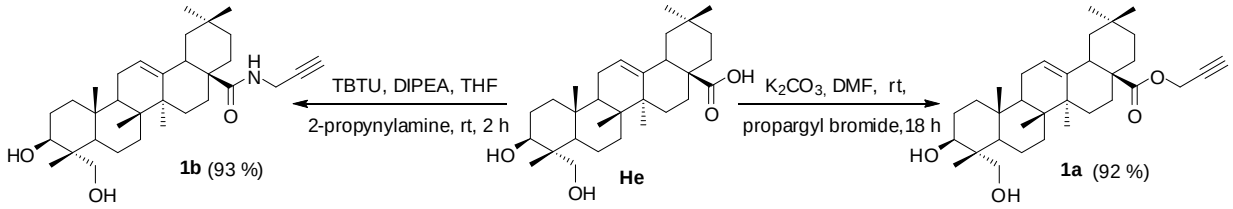
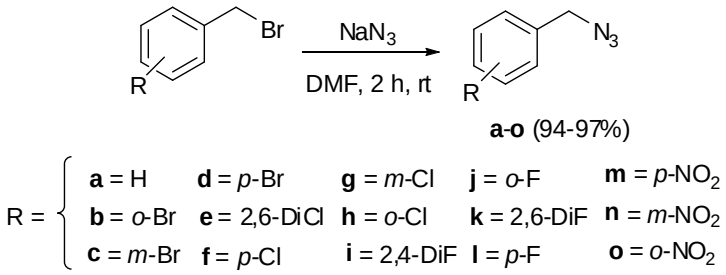


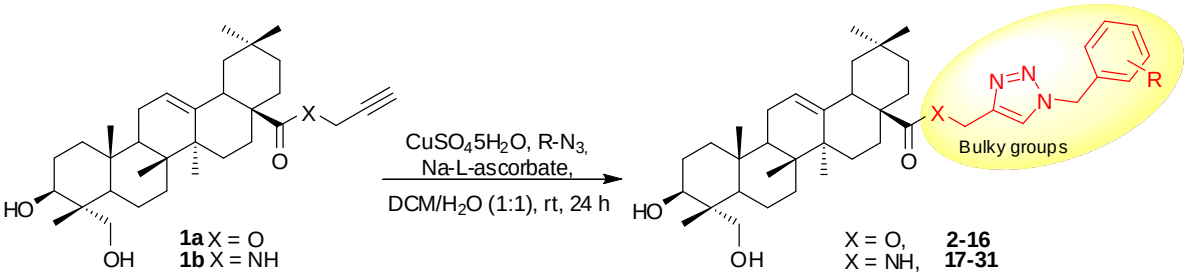
Figure 2. Cytotoxicity for **He**, and esters **4, 8** and **15** for all cells lines tested (melanoma cells - 518A2; ovarian carcinoma - A2780; colon adenocarcinoma - HT29; breast adenocarcinoma - MCF7; lung cancer - A549; thyroid carcinoma - 8505C.



Scheme 1. Synthesis of hederagenin alkyne derivatives **1a** and **1b**.



Scheme 2. Synthesis of substituted benzyl azides (**a**-**o**).



X	R	Compound (%)	X	R	Compound (%)
O	H	**2** (60)	NH	H	**17** (90)
O	*o*-Br	**3** (91)	NH	*o*-Br	**18** (85)
O	*m*-Br	**4** (65)	NH	*m*-Br	**19** (90)
O	*p*-Br	**5** (91)	NH	*p*-Br	**20** (95)
O	2,6-Cl	**6** (84)	NH	2,6-Cl	**21** (75)
O	*p*-Cl	**7** (33)	NH	*p*-Cl	**22** (81)
O	*m*-Cl	**8** (90)	NH	*m*-Cl	**23** (78)
O	*o*-Cl	**9** (54)	NH	*o*-Cl	**24** (79)
O	2,4-F	**10** (89)	NH	2,4-F	**25** (84)
O	*o*-F	**11** (85)	NH	*o*-F	**26** (70)
O	2,6-F	**12** (67)	NH	2,6-F	**27** (97)
O	*p*-F	**13** (77)	NH	*p*-F	**28** (70)
O	*p*-NO_2	**14** (44)	NH	*p*-NO_2	**29** (66)
O	*m*-NO_2	**15** (52)	NH	*m*-NO_2	**30** (79)
O	*o*-NO_2	**16** (76)	NH	*o*-NO_2	**31** (76)

Scheme 3. Synthesis of hederagenin 1,2,3-trizolyl derivatives **2-31**

Highlights

- A series of novel aryl-1*H*-1,2,3-triazol-4-ylesters and amides derivatives of hederagenin has been synthesized
- Some derivatives were more active for six human cancer lines than hederagenin.
- EC_{50} values for *m*-Br, *m*-Cl and *m*-NO_2 ester derivatives ranged 3.0 to 4.1 µM
- An ester derivative carrying an *o*-F group was the most cytotoxic compound against HT29 cells showing EC_{50} = 1.6 µM, with a IS = 5.4.