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¹Solid-Phase Library Synthesis of Bi-Functional Derivatives of ²Oleanolic and Maslinic Acids and Their Cytotoxicity on Three Cancer ³Cell Lines

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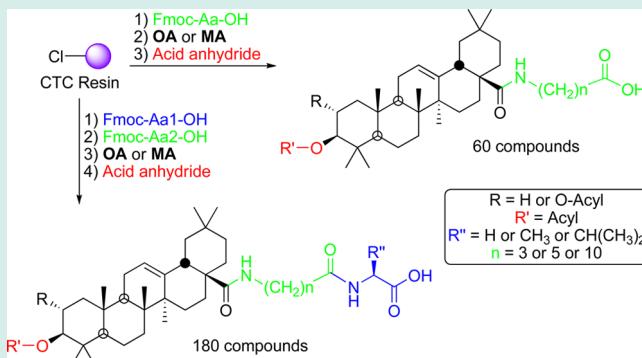
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11 Supporting Information

ABSTRACT: A wide set of 264 compounds has been semisynthesized with high yields and purities. These compounds have been obtained through easy synthetic processes based on a solid-phase combinatorial methodology. All the members of this library have one central core of a natural pentacyclic triterpene (oleanolic or maslinic acid) and differ by 6 amino acids, coupled with the carboxyl group at C-28 of the triterpenoid skeleton, and by 10 different acyl groups attached to the hydroxyl groups of the A-ring of these molecules. According to the literature on the outstanding and promising pharmacological activities of other similar terpene derivatives, some of these compounds have been tested for their cytotoxic effects on the proliferation of three cancer cell lines: B16–F10, HT29, and Hep G2. In general, we have found that around 70% of the compounds tested show cytotoxicity in all three of the cell lines selected; around 60% of the cytotoxic compounds are more effective than their corresponding precursors, that is, oleanolic (OA) or maslinic (MA) acids; and nearly 50% of the cytotoxic derivatives have IC₅₀ values between 2- to 320-fold lower than their corresponding precursor (OA or MA).

KEYWORDS: *combinatorial chemistry, solid-phase synthesis, triterpene, acylation, oleanolic, maslinic*



30 ■ INTRODUCTION

Natural products play a major role in drug development and chemical biology.^{1–3} In fact, nearly half of the new drugs introduced into the market in the last three decades have been natural products or their derivatives.^{4,5} Natural products are promising scaffolds for diversification by using combinatorial methods to establish several libraries of products offering potentially valuable activities.^{6–8}

Combinatorial chemistry is a quick and very useful tool for the semisynthesis of thousands of organic compounds with potential pharmacological activities.^{9,10} In the past few decades, a large number of combinatorial libraries have been constructed, and they significantly supplement the chemical diversity of the traditional collections of potentially active medicinal compounds.¹¹ The development of high-throughput screenings based on molecular targets has led to a demand for the generation of large libraries of compounds to satisfy the enormous capacities of these screens. Combinatorial chemistry was envisioned as the answer to this demand, initially focusing

on the synthesis of peptide and oligonucleotide libraries but is now reported to be shifting its focus to the synthesis of small, drug-like molecules.¹²

Solid-phase synthesis has been used to enrich combinatorial chemistry libraries; through the use of solid supports and their modified forms.^{13–15} Progress in solid-phase organic synthesis has enabled the current combination of natural-product synthesis with combinatorial methods. The strategy most frequently followed has been to attach a natural product core structure to a solid phase and subsequently modify the functional groups. Solid-phase organic synthesis has emerged as a powerful tool in the synthesis of small molecules as a means of exploiting combinatorial chemistry to discover new effective products.^{16,17}

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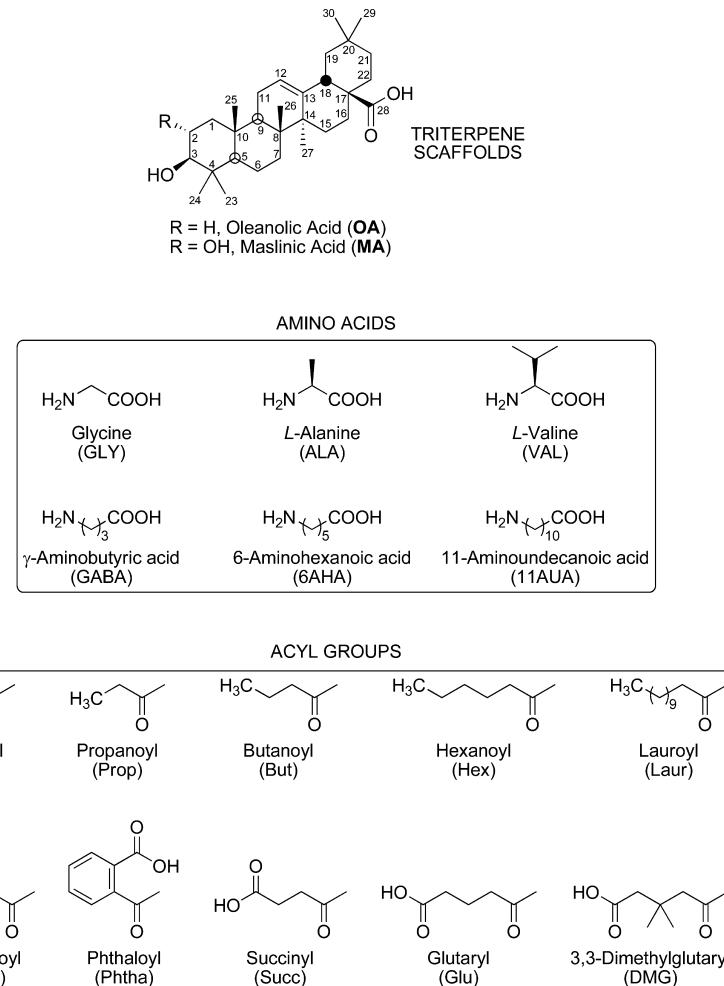


Figure 1. Triterpene scaffolds and structures of the amino acids and acyl groups used for the construction of the library of the OA or MA derivatives.

63 Triterpenoids, natural substances present in many plants in
64 nature, belong to a wide family of compounds obtained
65 biosynthetically by cyclic reactions from squalene. Biologically,
66 the most important triterpenoid structures are oleanane, ursane,
67 lupane, and dammarane triterpenoids.¹⁸ These compounds are
68 used in conventional medicine for their anti-inflammatory,
69 hepatoprotective, analgesic, antimicrobial, virostatic, anticancer,
70 and anti-HIV effects.^{19–30} Chemical modifications of these
71 natural triterpene compounds have resulted in products that
72 have improved the biological activities of their precursors.^{31–33}
73 In recent years, much work has been focused on modifying
74 several triterpenic acids at the C-3 or C-28 positions, forming
75 acyl or amino acid derivatives, in order to increase their
76 hydrosolubility and biological activity.^{34–43} In this sense, we
77 have performed the solution- or solid-phase semisynthesis of
78 several C-3 and C-28 derivatives of oleanolic or maslinic acid.
79 We have evaluated them for their antiproliferative and antiviral
80 effects, finding promising results as anticancer and as anti-HIV
81 agents.^{44–46}

82 Oleanolic (3β -hydroxyolean-12-en-28-oic acid, OA)^{47,48} and
83 maslinic ($2\alpha,3\beta$ -dihydroxyolean-12-en-28-oic acid, MA)⁴⁹ acids,
84 which belong to these kinds of natural products with
85 remarkable biological properties^{50–52} are widely found in
86 nature and are present in high concentrations in olive-pomace
87 oil, being the main components of the protective wax-like
88 coating of the olive skin. A method of producing large amounts

of both compounds from these solid wastes has been reported⁸⁹ by our group.⁵³

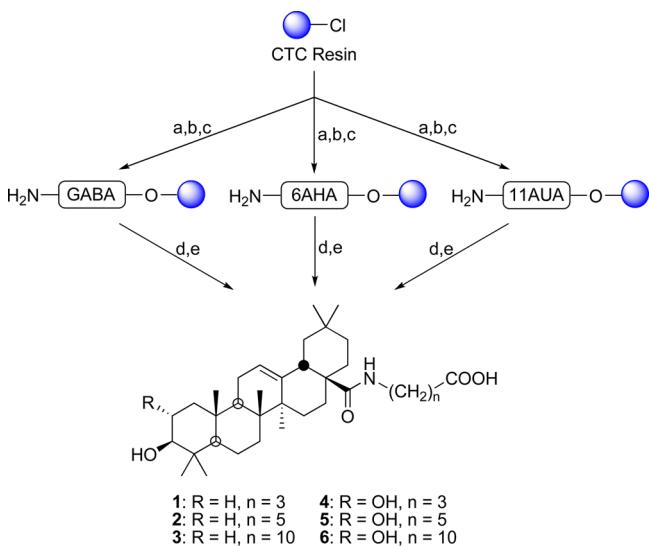
In this work, we have semisynthesized a library of 240⁹¹ compounds, through combinatorial solid-phase procedures,⁹² using the above-mentioned two natural triterpene acids (OA or⁹³ MA) as scaffolds. These compounds are bifunctional OA or⁹⁴ MA derivatives, formed by the combinatorial attachment of 6⁹⁵ different amino acids to the carboxylic group at C-28 of the⁹⁶ triterpene, and subsequent acylation with 10 different acid⁹⁷ anhydrides in the hydroxyl groups of the A-ring of the⁹⁸ triterpene skeleton. We have also examined the cytotoxic effects⁹⁹ of these OA or MA derivatives on the proliferation of three¹⁰⁰ cancer cell lines: HT29, Hep G2, and B16-F10. One of our¹⁰¹ main objectives has been to find new triterpene derivatives with¹⁰² greater cytotoxic and antitumor properties than the natural¹⁰³ compounds from which they derive. We have explored the¹⁰⁴ importance of the polarity, molecular volume, and substituent¹⁰⁵ position in the cytotoxicity induced by these triterpenes¹⁰⁶ derivatives of OA or MA. Agents that suppress the proliferation¹⁰⁷ of malignant cells, by inducing cytotoxic effects, may represent¹⁰⁸ a useful mechanistic approach to chemoprevention and¹⁰⁹ chemotherapy of cancer. With these effects, these new¹¹⁰ triterpene derivatives may provide a useful new strategy for¹¹¹ different types of cancer.

113 ■ RESULTS AND DISCUSSION

114 The triterpene scaffolds represent a promising pharmacophore
 115 for synthesizing libraries to obtain derivatives with improved
 116 biological activities. Thus, to prepare a broad library of acyl-
 117 triterpene-amino-acid derivatives, we used as carbon scaffolds:
 118 oleanolic acid (OA) or maslinic acid (MA), two natural
 119 triterpene acids from olive-oil industry residues; 6 amino acids
 120 (glycine, GLY; alanine, ALA; valine, VAL; γ -aminobutyric acid,
 121 GABA; 6-aminohexanoic acid, 6AHA; 11-aminoundecanoic
 122 acid, 11AUA); and 10 acid anhydrides (acetic, propanoic,
 123 butanoic, hexanoic, lauric, benzoic, phthalic, succinic, glutaric,
 124 and 3,3-dimethylglutaric anhydrides) (Figure 1). The above-
 125 mentioned triterpenoids show two-point diversity: the C-28
 126 carboxyl group and one or two hydroxyl groups in the A-ring of
 127 the triterpene skeleton. The cited amino acids were attached to
 128 the C-28 carboxyl group, and subsequently, the hydroxyl
 129 groups at C-2 (for OA) or at C-2 and C-3 (for MA) were
 130 acylated with the 10 above-described acid anhydrides, to
 131 introduce more diversity into these compounds, following
 132 appropriate solid-phase protocols in both processes.

133 **Peptide Conjugation.** The semisynthesis of the library of
 134 these compounds commenced with the solid-phase construc-
 135 tion of the mono- or dipeptidyl OA or MA derivatives (1–24)
 136 (Schemes 1 and 2). Our solid-phase strategy was initially

137 **Scheme 1. Semi-synthesis of Monopeptidyl OA (1–3) or MA
 138 (4–6) Derivatives^a**

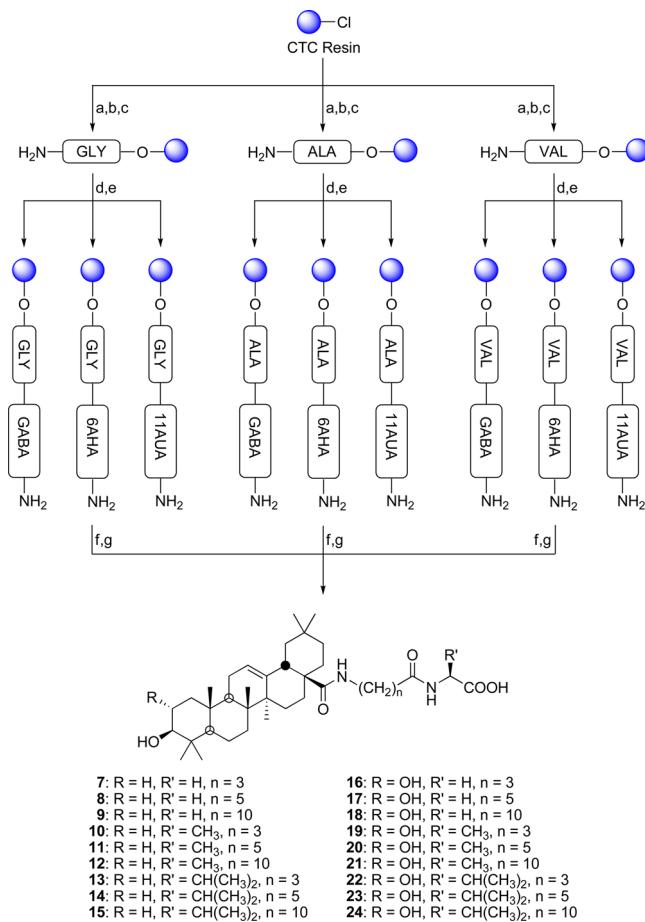


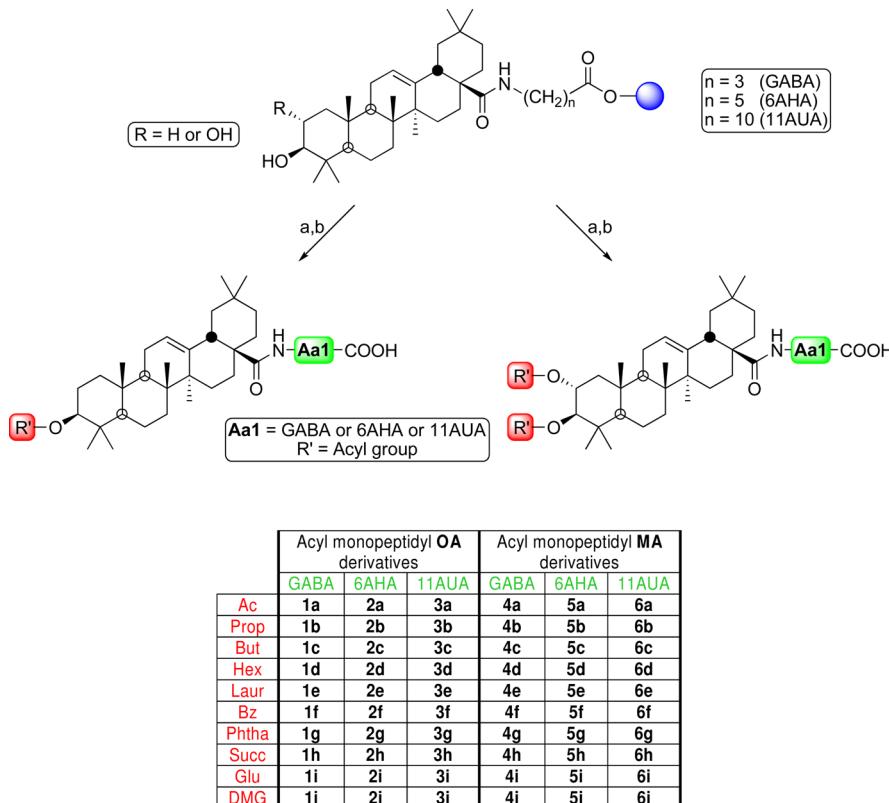
^aReagents and conditions: (a) Fmoc-GABA-OH, Fmoc-6AHA-OH, or Fmoc-11AUA-OH, DIEA, DCM; (b) MeOH; (c) piperidine-DMF (1:4); (d) OA or MA, PyAOP, HOAt, DIEA, DMF; (e) TFA-DCM (1:99).

139 focused on the coupling of one or two amino acid fragments
 140 with the carboxyl group at C-28 of the triterpene skeleton. For
 141 these solid-phase reactions we chose the 2-chlorotriptyl chloride
 142 polymer resin (CTC-resin) as a solid support. This resin, which
 143 allows the release of compounds by treatment with low
 144 concentrations of acid, is the only one suitable for the
 145 preparation of OA or MA derivatives, because these triterpene
 146 acids are not totally stable at high TFA concentrations.

147 To obtain the monopeptidyl derivatives of OA (1–3) or MA
 148 (4–6), we prepared six syringes with 100 mg each one of the
 149 CTC-resin. After washing with DMF and DCM, and with an

150 **Scheme 2. Semi-synthesis of dipeptidyl OA (7–15) or MA
 151 (16–24) derivatives^a**



Scheme 3. Semi-synthesis of Monopeptidyl OA or MA Acyl Derivatives (1a–1j to 6a–6j).^a

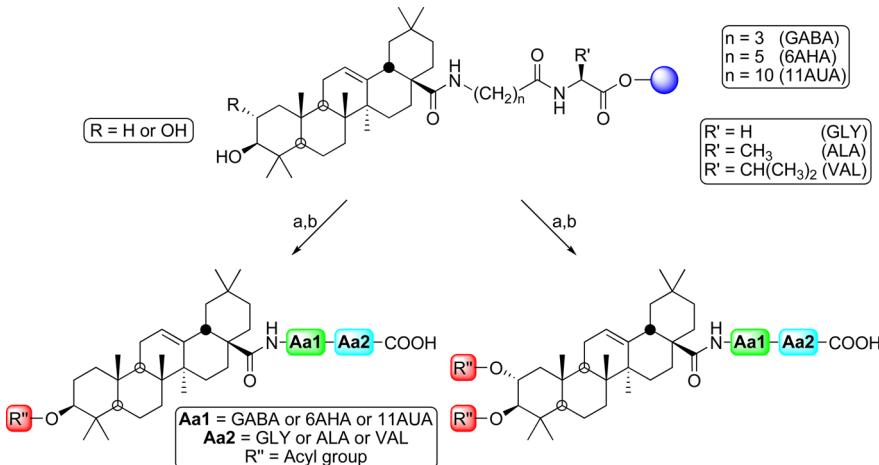
^aReagents and conditions: (a) Acid anhydride, Et₃N, DMAP, DMF, DCM; (b) TFA-DCM (1:99).

171 triterpene and the amino group of the corresponding amino
 172 acid. These signals invariably appeared as double doublets at δ_H
 173 6.10–6.20 for compounds 1–3 (in Cl₃CD) and δ_H 7.20–7.30
 174 for compounds 4–6 (in DMSO-*d*₆). In their ¹³C NMR spectra,
 175 two signals of carboxyl groups were present, one more
 176 deshielded, corresponding to the carbon atom of the peptide
 177 bond, and another less deshielded, corresponding to the free
 178 carboxyl group of the amino acid.

179 In a similar way, the dipeptidyl OA (7–15) or MA (16–24)
 180 derivatives were prepared attaching two amino acids to the
 181 carboxyl group at C-28 of the triterpene (Scheme 2). The
 182 synthesis started by putting three portions of CTC-resin into
 183 three syringes (labeled A, B, and C). Working as indicated
 184 above, we added Fmoc-GLY-OH, Fmoc-ALA-OH, or Fmoc-
 185 VAL-OH, to the syringes A, B, and C, respectively, stirring the
 186 mixture at rt for 1.5 h. Afterward, the above-mentioned
 187 capping, washing, and deprotecting processes were performed
 188 on the three syringes, whereupon each syringe was split into
 189 three identical aliquots (Scheme 2).

190 The nine fractions of monopeptidyl-resin thus obtained, were
 191 then treated with the three ω -amino acids: Fmoc-GABA-OH
 192 (syringes A-1, B-1, and C-1), Fmoc-6AHA-OH (syringes A-2,
 193 B-2, and C-2), and Fmoc-11AUA-OH (syringes A-3, B-3, and
 194 C-3). For these reactions, HOAt and DIPCDI were used as
 195 couplings agents. After 1.5 h of orbital stirring at rt, the
 196 ninhydrin test proved negative in all the syringes. Then, each
 197 dipeptidyl-resin was again subjected to the above-mentioned
 198 removal of the Fmoc group and washing processes. At this
 199 time, i.e. of the solid-phase reaction sequence, each syringe was
 200 again split into two identical portions to couple each dipeptidyl-
 201 resin with the triterpene acids (OA or MA; Scheme 2). These

coupling reactions were performed in the presence PyAOP, 202
 HOAt, and DIEA. After 24 h of reaction at rt and orbital 203
 stirring, the ninhydrin test proved negative in all the syringes, 204
 and each dipeptidyl OA (7–15) or MA (16–24) derivative was 205
 cleaved from its solid support by treatment with TFA/DCM. 206
 These derivatives were lyophilized, weighed, and analyzed by 207
 HPLC, determining their retention times, reaction yields, and 208
 purities, which were consistently higher than 90% (see 209
 Experimental Section). The structures of the dipeptidyl 210
 derivatives of OA (7–15) or MA (16–24) were also 211
 determined from their ¹H and ¹³C NMR data by comparison 212
 with those of their corresponding precursors (OA or MA). In 213
 these derivatives, the most significant differences in the signals 214
 of the NMR spectra were those of the amide groups occurring 215
 between the carboxyl group at C-28 of the triterpene and the 216
 amino group of the corresponding ω -amino acid (GABA, 217
 6AHA, or 11AUA), and between the carboxyl group of these ω - 218
 amino acids and the amino group of the corresponding α - 219
 amino acids (GLY, ALA, or VAL). The most deshielded NH 220
 signals appeared as double doublets at δ_H 7.50–6.30 for 221
 compounds 7–15 (in Cl₃CD), and around δ_H 8.00 for 222
 compounds 16–24 (in DMSO-*d*₆), corresponding to the α - 223
 amino acids. The other NH signals were situated at δ_H 6.50– 224
 6.10 for the OA derivatives (7–15) and around δ_H 7.20 for the 225
 MA derivatives (16–24), and corresponded to the ω -amino 226
 acids. In the ¹³C NMR spectra of all these derivatives, there 227
 were three signals of carboxyl group: the peptide group formed 228
 between the carboxyl group at C-28 and the amino group of the 229
 ω -amino acids (around δ_C 180, 7–15; δ_C 176, 16–24), the 230
 peptide group between the ω - and the α -amino acids (around 231
 δ_C 175, for OA derivatives; δ_C 174–172, for MA derivatives), 232

Scheme 4. Semi-synthesis of Dipeptidyl OA or MA Acyl Derivatives (7a–7j to 24a–24j)^a

	Acyl dipeptidyl OA derivatives								
	GABA GLY	6AHA GLY	11AUA GLY	GABA ALA	6AHA ALA	11AUA ALA	GABA VAL	6AHA VAL	11AUA VAL
Ac	7a	8a	9a	10a	11a	12a	13a	14a	15a
Prop	7b	8b	9b	10b	11b	12b	13b	14b	15b
But	7c	8c	9c	10c	11c	12c	13c	14c	15c
Hex	7d	8d	9d	10d	11d	12d	13d	14d	15d
Laur	7e	8e	9e	10e	11e	12e	13e	14e	15e
Bz	7f	8f	9f	10f	11f	12f	13f	14f	15f
Phtha	7g	8g	9g	10g	11g	12g	13g	14g	15g
Succ	7h	8h	9h	10h	11h	12h	13h	14h	15h
Glu	7i	8i	9i	10i	11i	12i	13i	14i	15i
DMG	7j	8j	9j	10j	11j	12j	13j	14j	15j

	Acyl dipeptidyl MA derivatives								
	16a	17a	18a	19a	20a	21a	22a	23a	24a
Ac	16a	17a	18a	19a	20a	21a	22a	23a	24a
Prop	16b	17b	18b	19b	20b	21b	22b	23b	24b
But	16c	17c	18c	19c	20c	21c	22c	23c	24c
Hex	16d	17d	18d	19d	20d	21d	22d	23d	24d
Laur	16e	17e	18e	19e	20e	21e	22e	23e	24e
Bz	16f	17f	18f	19f	20f	21f	22f	23f	24f
Phtha	16g	17g	18g	19g	20g	21g	22g	23g	24g
Succ	16h	17h	18h	19h	20h	21h	22h	23h	24h
Glu	16i	17i	18i	19i	20i	21i	22i	23i	24i
DMG	16j	17j	18j	19j	20j	21j	22j	23j	24j

^aReagents and conditions: (a) Acid anhydride, Et₃N, DMAP, DMF, DCM; (b) TFA-DCM (1:99).

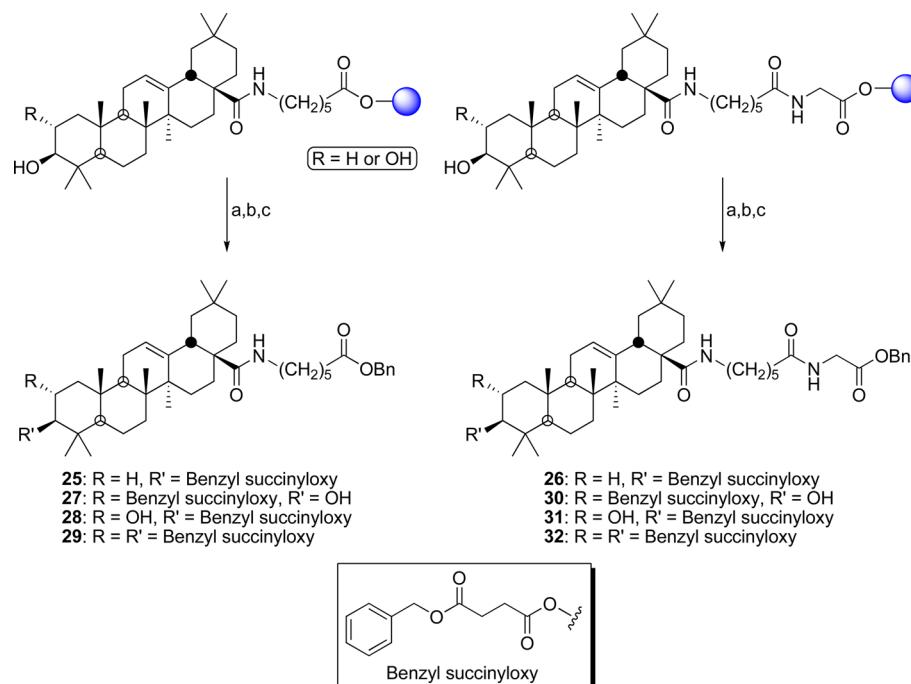
and the free carboxyl group of the α -amino acids (around δ_{C} 174–172 for all derivatives).

Acylation Reaction. In an effort to increase the diversity of this type of compounds, these mono- or dipeptidyl OA or MA derivatives (**1–24**) were acylated in the hydroxyl groups at C-3 or C-2/C-3 of the A-ring of the triterpene skeleton. These acylation reactions were performed in solid phase with 10 selected acid anhydrides in the presence of Et₃N and DMAP as catalysts (Schemes 3 and 4). The 10 acid anhydrides for these acylation processes (Figure 1) had diverse physical and chemical properties. In this sense, several acid anhydrides were chosen with aliphatic carbon chains of different lengths or with an aromatic ring, and also cyclic acid anhydrides, which originated acyl groups with an additional terminal carboxyl group. Thus, 10 portions of the monopeptidyl derivatives of OA (**1–3**) were prepared as previously described and, before being cleaved from de CTC-resin; they were treated with the above-mentioned 10 acid anhydrides, and were subsequently cleaved from the solid support by treatment with TFA/DCM, collected, and lyophilized. Thus, 30 new 3-acylated-28-monopeptidyl AO derivatives (**1a–1j**, **2a–2j**, and **3a–3j**) (Scheme 3) were obtained and analyzed by HPLC and HRMS.

In all the cases, their purities were higher than 90% and their molecular masses were consistent with the expected structures (see Experimental Section and Supporting Information). In a similar way, the MA monopeptidyl derivatives (**4–6**) were acylated with an excess of the above-mentioned 10 acid anhydrides, to obtain mainly the doubly acylated compound at the hydroxyl groups at C-2 and C-3 of the A-ring of MA. Thus, we obtained 30 new 2,3-diacylated-28-monopeptidyl MA derivatives (**4a–4j**, **5a–5j**, and **6a–6j**) (Scheme 3), which were also analyzed by HPLC and HRMS. The observed purities for these derivatives were high (around 90–100%), except for the dicarboxylic acyl derivatives (phthaloyl, succinyl, glutaryl, and 3,3-dimethylglutaryl), for which the reaction yields were slightly lower (range 75–100%) (see Experimental Section and Supporting Information).

Similarly, starting from the dipeptidyl OA derivatives (**7–15**) or the dipeptidyl MA derivatives (**16–24**), and according with the above-described acylation methodology, 90 new 3-acylated-28-dipeptidyl OA derivatives (**7a–7j** to **15a–15j**), and another 90 new 2,3-diacylated-28-dipeptidyl MA derivatives (**16a–16j** to **24a–24j**), were prepared (Scheme 4). Also, these derivatives had great purities (90–100%), again with the exception of the

Scheme 5. Solid-Phase Succinylation Reactions and Consecutive Solution-Phase Benzylation Reactions of Mono- or Dipeptidyl Derivatives of OA or MA.^a



^aReagents and conditions: (a) Acid anhydride, Et₃N, DMAP, DMF, DCM; (b) TFA-DCM (1:99); (c) BnCl, K₂CO₃, DMF.

277 dicarboxylic acyl derivatives (**16g–16j** to **24g–24j**, 75–100%),
278 as detected in their HPLC analyses, and presented appropriate
279 HRMS spectra (see Experimental Section and Supporting
280 Information).

281 **Quantification of Succinyl Derivatives.** In these solid-
282 phase acylation studies, we found that the mono- or dipeptidyl
283 OA or MA acyl derivatives that were achieved from a cyclic acid
284 anhydride (phthalic, succinic, glutaric, or 3,3-dimethylglutaric)
285 were compounds of very difficult chromatographic isolation
286 and also of complicated spectroscopic identification because of
287 the presence of two or three free carboxylic groups in the
288 molecule. Therefore, to avoid these experimental problems and
289 to determine more accurately the proportion of these
290 derivatives obtained by solid-phase synthesis, we selected
291 several succinyl derivatives to protect the free carboxylic acid
292 groups through a benzylation reaction. Thus, following the
293 process of solid-phase synthesis described in this work, we
294 achieved *N*-(3 β -succinylxyloxyolean-12-en-28-oyl)-6-aminohexa-
295 noic acid (**2h**) and *N'*-[*N*-(3 β -succinylxyloxyolean-12-en-28-oyl)-
296 6-aminohexanoyl]-glycine (**8h**), respectively. Both compounds
297 were benzylated separately with benzyl chloride giving benzyl
298 *N*-(3 β -benzylsuccinylxyloxyolean-12-en-28-oyl)-6-aminohexa-
299 noate (**25**, 95%) and benzyl *N'*-[*N*-(3 β -benzylsuccinylxyloxy-
300 lean-12-en-28-oyl)-6-aminohexanoyl]-glycinate (**26**, 98%), re-
301 spectively (Scheme 5). The NMR spectra of **25** and **26**,
302 compared with those of their corresponding precursors (**2h** or
303 **8h**) presented the signals of two benzyl groups (around δ_H 7.35
304 and 5.15, and δ_C 136–128 and 67).

305 Similarly, we studied the protection of the free carboxylic
306 acid groups of several succinyl derivatives of mono- or
307 dipeptidyl MA compounds, through a benzylation reaction
308 with benzyl chloride. In these case, not only the 2,3-disuccinyl
309 derivatives (**5h** and **17h**, respectively) were detected, but also
310 the 2- and 3-succinyl derivatives. Consequently, three

311 benzylated derivatives were identified respectively: the 2 α -
312 benzylsuccinyl (**27**, 4%; **30**, 5%), the 3 β -benzylsuccinyl (**28**,
313 2%; **31**, 2%), and the 2 α ,3 β -dibenzylsuccinyl derivatives (**29**,
314 80%; **32**, 85%) (Scheme 5). Major NMR spectroscopic
315 differences between these benzylated compounds were the
316 chemical shifts of the signals of H-2 and H-3 of the A-ring of
317 these molecules, which depended on whether the substituents
318 were benzylated or not at these positions. Therefore, by
319 forming these benzylated derivatives we could determine more
320 accurately the proportion of succinylated derivatives obtained
321 by solid-phase synthesis.

322 **Cytotoxicity Tests.** Cytotoxicity effects have been
323 previously described in a wide variety of pentacyclic triterpenes,
324 involving a mechanism that implied MAPK (mitogen-activated
325 protein kinases), death receptor, and mitochondrial disrupt-
326 tion.^{25,54} We tested the cytotoxicity of 90 compounds of the
327 264 semisynthesized derivatives, on three cell lines (B16–F10,
328 HT29, and Hep G2) (Figure 2). These compounds were
329 selected to draw consistent conclusions concerning the
330 structure–activity relationship of these types of triterpene
331 derivatives. In general, we found that, under the conditions
332 assayed (from 0 to 300 μ g/mL), nearly 90% of the compounds
333 assayed showed cytotoxicity on the B16–F10 and HT29 cell
334 lines, while on the Hep G2 cell line this percentage decreased

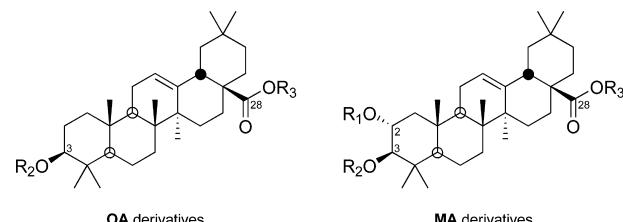


Figure 2. General structures of the tested OA or MA derivatives.

Table 1. Growth-Inhibitory Effects of the Mono- (1–6) or Dipeptidyl (7–24) OA or MA Derivatives on the Three Cancer Cell Lines

compound	R ₁	R ₂	R ₃	B16-F10 ^a	IC ₅₀ of precursor ^b /IC ₅₀ of compound	HT29 ^a	IC ₅₀ of precursor ^b /IC ₅₀ of compound	Hep G2 ^a	IC ₅₀ of precursor ^b /IC ₅₀ of compound
OA	H	H		106.4 ± 3.7	1.0	429.9 ± 0.7	1.0	211.8 ± 0.5	1.0
1	H	GABA		185.0 ± 9.4	0.6	137.2 ± 3.5	3.1	268.4 ± 10.6	0.8
2	H	6AHA		115.5 ± 8.2	0.9	84.8 ± 3.0	5.1	110.9 ± 0.2	1.9
3	H	11AUA		108.2 ± 1.6	1.0	120.4 ± 3.1	3.6	80.5 ± 2.9	2.6
7	H	GABA-GLY		290.2 ± 14.1	0.4	170.3 ± 4.2	2.5	216.0 ± 17.4	1.0
8	H	6AHA-GLY		111.3 ± 1.4	1.0	132.9 ± 0.6	3.2	182.4 ± 1.4	1.2
9	H	11AUA-GLY		>500		194.8 ± 1.6	2.2	>500	
10	H	GABA-ALA		356.1 ± 12.7	0.3	243.1 ± 2.4	1.8	232.3 ± 5.9	0.9
11	H	6AHA-ALA		115.5 ± 4.9	0.9	142.1 ± 2.8	3.0	175.4 ± 5.6	1.2
12	H	11AUA-ALA		340.5 ± 0.1	0.3	189.6 ± 3.5	2.3	>500	
13	H	GABA-VAL		79.4 ± 0.4	1.3	170.9 ± 2.7	2.5	125.9 ± 2.8	1.7
14	H	6AHA-VAL		105.3 ± 2.4	1.0	124.0 ± 1.3	3.5	134.1 ± 2.8	1.6
15	H	11AUA-VAL		71.9 ± 1.0	1.5	73.6 ± 2.1	5.8	88.2 ± 7.6	2.4
MA	H	H	H	36.2 ± 2.5	1.0	32.2 ± 3.8	1.0	99.2 ± 15.5	1.0
4	H	H	GABA	180.3 ± 3.9	0.2	86.4 ± 1.4	0.4	202.4 ± 4.1	0.5
5	H	H	6AHA	178.4 ± 0.9	0.2	137.9 ± 0.7	0.2	107.0 ± 5.4	0.9
6	H	H	11AUA	102.7 ± 1.0	0.4	116.3 ± 5.8	0.3	54.7 ± 3.2	1.8
16	H	H	GABA-GLY	469.6 ± 3.8	0.1	242.6 ± 3.1	0.1	>500	
17	H	H	6AHA-GLY	263.5 ± 1.8	0.1	218.7 ± 0.7	0.1	>500	
18	H	H	11AUA-GLY	103.0 ± 5.9	0.4	175.5 ± 3.5	0.2	124.0 ± 6.3	0.8
19	H	H	GABA-ALA	351.9 ± 12.2	0.1	208.5 ± 1.2	0.2	>500	
20	H	H	6AHA-ALA	223.4 ± 4.0	0.2	162.6 ± 1.1	0.2	>500	
21	H	H	11AUA-ALA	62.2 ± 1.4	0.6	129.4 ± 10.3	0.2	88.5 ± 0.4	1.1
22	H	H	GABA-VAL	243.3 ± 3.9	0.1	181.9 ± 3.5	0.2	>500	
23	H	H	6AHA-VAL	164.0 ± 2.9	0.2	150.4 ± 3.6	0.2	292.9 ± 2.6	0.3
24	H	H	11AUA-VAL	39.6 ± 1.0	0.9	47.4 ± 1.0	0.7	53.2 ± 1.1	1.9

^aThe IC₅₀ values (μM) were calculated considering control untreated cells as 100% of viability. Cell-growth inhibition was analyzed by the MTT assay, as described in the Experimental Procedures. All assays were made two times using three replicates. Values, means ± SEM. ^bThese columns represent the ratio between the IC₅₀ of each precursor (OA or MA) and the IC₅₀ of the related derivatives.

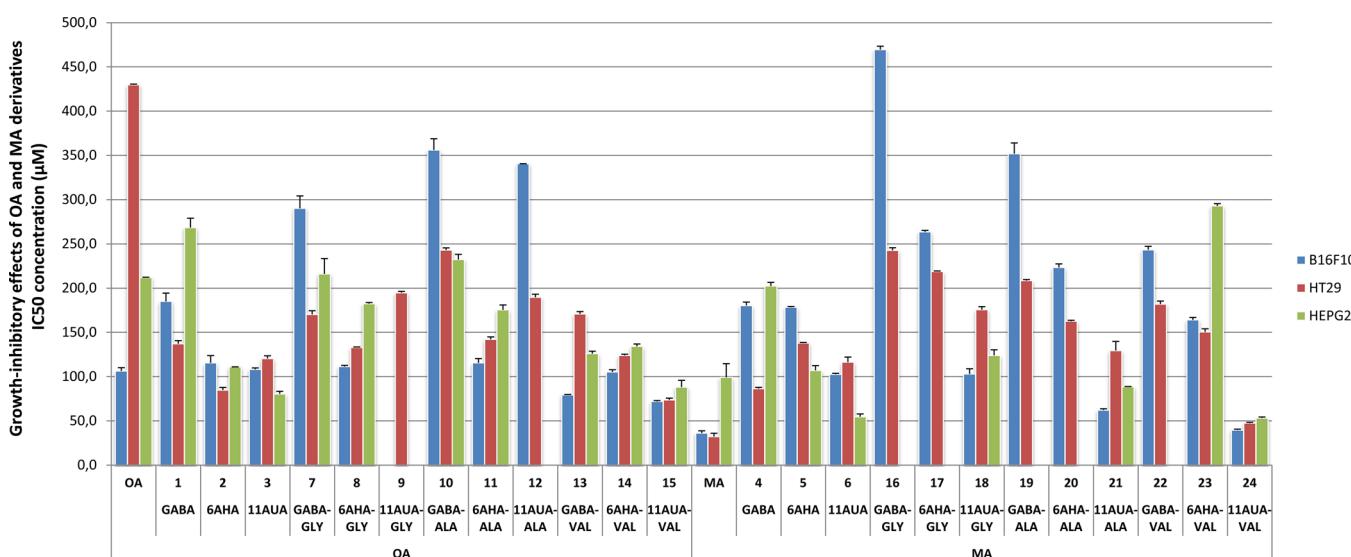
Chart 1. Growth-Inhibitory Effects (IC₅₀, μM) of the Mono- or Dipeptidyl OA or MA Derivatives on the Three Cancer Cell Lines

Table 2. Growth-Inhibitory Effects of the Mono- (**1g–6g**) or Dipeptidyl (**7g–24g**) OA or MA Phthaloyl Derivatives on the Three Cancer Cell Lines

compound	R ₁	R ₂	R ₃	B16–F10 ^a	IC ₅₀ of precursor ^b /IC ₅₀ of compound	HT29 ^a	IC ₅₀ of precursor ^b /IC ₅₀ of compound	Hep G2 ^a	IC ₅₀ of precursor ^b /IC ₅₀ of compound
OA		H	H	106.4 ± 3.7	1.0	429.9 ± 0.7	1.0	211.8 ± 0.5	1.0
1g		Phtha	GABA	211.7 ± 1.1	0.5	314.5 ± 1.5	1.4	326.8 ± 4.4	0.6
2g		Phtha	6AHA	140.0 ± 21.2	0.8	213.7 ± 3.1	2.0	211.3 ± 2.5	1.0
3g		Phtha	11AUA	68.6 ± 0.7	1.6	113.5 ± 0.4	3.8	79.3 ± 1.0	2.7
7g		Phtha	GABA-GLY	>500		>500		>500	
8g		Phtha	6AHA-GLY	>500		399.8 ± 1.7	1.1	>500	
9g		Phtha	11AUA-GLY	76.8 ± 2.4	1.4	167.0 ± 2.4	2.6	125.9 ± 2.9	1.7
10g		Phtha	GABA-ALA	>500		398.2 ± 1.1	1.1	>500	
11g		Phtha	6AHA-ALA	314.5 ± 2.0	0.3	>500		>500	
12g		Phtha	11AUA-ALA	122.0 ± 2.8	0.9	160.5 ± 3.5	2.7	129.6 ± 2.4	1.6
13g		Phtha	GABA-VAL	211.4 ± 3.7	0.5	275.9 ± 0.2	1.6	327.9 ± 3.0	0.6
14g		Phtha	6AHA-VAL	134.2 ± 1.1	0.8	364.4 ± 3.2	1.2	>500	
15g		Phtha	11AUA-VAL	82.3 ± 2.1	1.3	143.8 ± 3.3	3.0	153.8 ± 2.7	1.4
MA	H	H	H	36.2 ± 2.5	1.0	32.2 ± 3.8	1.0	99.2 ± 15.5	1.0
4g	Phtha	Phtha	GABA	348.3 ± 3.9	0.1	357.0 ± 0.6	0.1	>500	
5g	Phtha	Phtha	6AHA	215.4 ± 1.0	0.2	336.5 ± 0.7	0.1	243.0 ± 1.3	0.4
6g	Phtha	Phtha	11AUA	129.7 ± 3.6	0.3	280.2 ± 3.4	0.1	213.7 ± 2.1	0.5
16g	Phtha	Phtha	GABA-GLY	>500		>500		>500	
17g	Phtha	Phtha	6AHA-GLY	>500		>500		>500	
18g	Phtha	Phtha	11AUA-GLY	59.1 ± 5.1	0.6	228.1 ± 0.9	0.1	>500	
19g	Phtha	Phtha	GABA-ALA	>500		>500		>500	
20g	Phtha	Phtha	6AHA-ALA	>500		>500		>500	
21g	Phtha	Phtha	11AUA-ALA	202.8 ± 1.6	0.2	>500		268.1 ± 2.7	0.4
22g	Phtha	Phtha	GABA-VAL	>500		>500		>500	
23g	Phtha	Phtha	6AHA-VAL	>500		>500		>500	
24g	Phtha	Phtha	11AUA-VAL	>500		>500		>500	

^aThe IC₅₀ values (μM) were calculated considering control untreated cells as 100% of viability. Cell-growth inhibition was analyzed by the MTT assay, as described in the Experimental Procedures. All assays were made two times using three replicates. Values, means ± SEM. ^bThese columns represent the ratio between the IC₅₀ of each precursor (OA or MA) and the IC₅₀ of the related derivatives.

335 to 67%. Several of these cytotoxic compounds, mostly OA
336 derivatives, were more effective than their corresponding
337 precursor (OA or MA), with percentages ranging from 31%
338 (B16–F10) to 58% (HT29) and up to 67% (Hep G2).

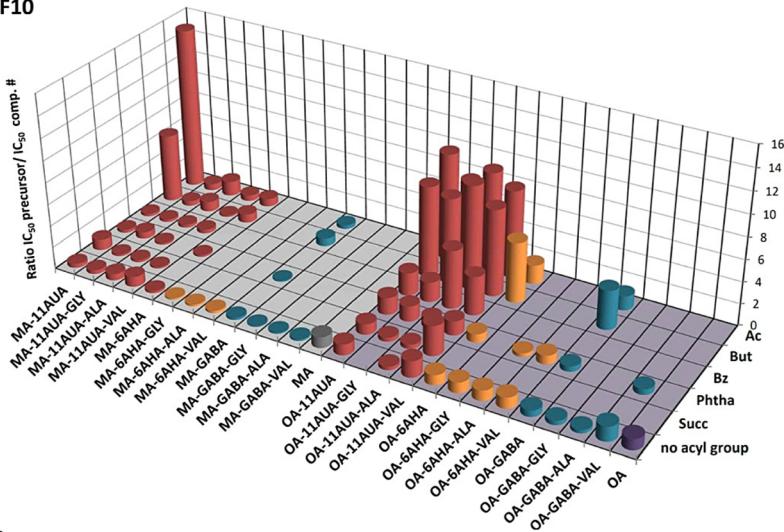
339 Comparing the IC₅₀ data for OA and MA on the three cell
340 lines selected, we deduce that the hydroxyl group at C-2
341 enhanced the cytotoxicity of the last one (Table 1 and Chart 1).
342 Moreover, the IC₅₀ values of the monopeptidyl OA derivatives
343 (**1–3**) were in general lower than that of OA, particularly when
344 the amino acid had a longer carbon chain (6AHA or 11AUA);
345 but the IC₅₀ data of the monopeptidyl MA derivatives (**4–6**)
346 were higher than that of MA, with the exception of the 11AUA-
347 MA derivative (**6**) with the Hep G2 cell line. Furthermore,
348 when amino acids having a greater length chain (11AUA) and a
349 larger volume (VAL) were used, the dipeptidyl OA (**15**) or MA

(**24**) derivatives exhibited the lowest cytotoxic concentrations 350
(Table 1 and Chart 1). 351

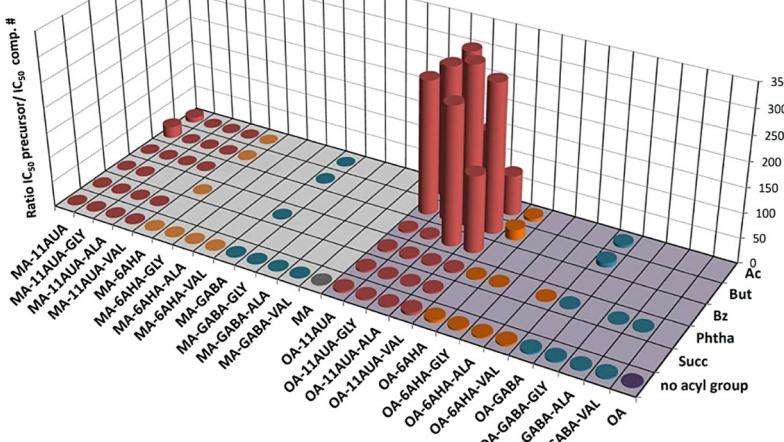
We also studied the cytotoxicity of the mono- (**1g–6g**) or 352
dipeptidyl (**7g–24g**) OA or MA phthaloyl derivatives (Table 2 353 t2
and Chart 2). These products were selected according with the 354 c2
very good results achieved with this acyl group with the same 355
triterpene compounds, in a previous work.⁴⁶ In this case, we 356
analyzed the influence of one or two amino acids, linked to the 357
carboxyl group at C-28 of the molecule, on the cytotoxicity of 358
these compounds. The best cytotoxic results with the phtaloyl 359
OA derivatives were achieved when a long-chain amino acid 360
(11AUA) was present in the molecule (**3g**, **9g**, **12g**, and **15g**). 361
However, the diphthaloyl MA derivatives registered worse 362
results than did MA (Table 2 and Chart 2). 363

Chart 2. Comparison of the Growth-Inhibitory Effects of the OA or MA Derivatives on the Three Cancer Cell Lines, Describing the Ratio between the IC₅₀ Values of the Triterpene Precursors (OA or MA) and the IC₅₀ Values of Their Cytotoxic Derivatives^a

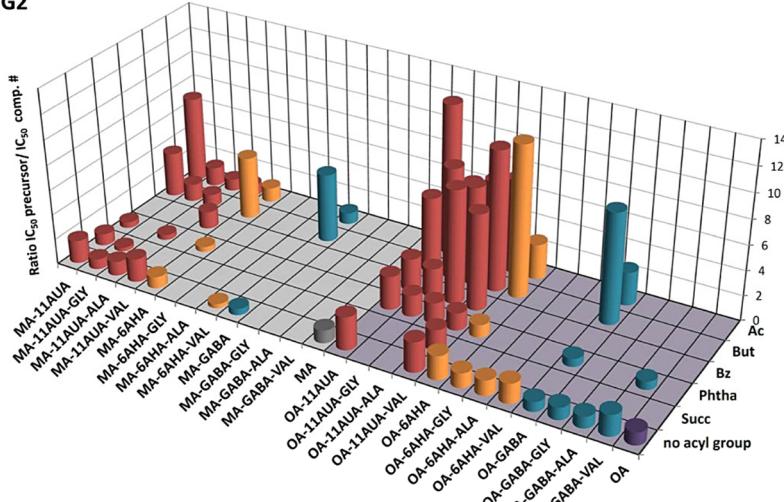
B16-F10



HT29



Hep G2



^aAc = acetyl, But = butanoyl, Bz = benzoyl, Phtha = phthaloyl, Succ = succinyl.

364 Finding good cytotoxicity results with the 11AUA derivatives
365 of OA or MA, we analyzed the influence of these monopeptidyl

(11AUA) or dipeptidyl (11AUA with GLY, ALA, or VAL) 366 derivatives with other acyl groups (acetyl, butanoyl, benzoyl, or 367

Table 3. Growth-Inhibitory Effects of the Mono- (11-AUA) or Dipeptidyl (11AUA with GLY, ALA, or VAL) OA or MA Acyl (ac, but, bz, or succ) Derivatives on the Three Cancer Cell Lines

compound	R ₁	R ₂	R ₃	B16-F10 ^a	IC ₅₀ of precursor ^b /IC ₅₀ of compound	HT29 ^a	IC ₅₀ of precursor ^b /IC ₅₀ of compound	Hep G2 ^a	IC ₅₀ of precursor ^b /IC ₅₀ of compound
OA	H	H		106.4 ± 3.7	1.0	429.9 ± 0.7	1.0	211.8 ± 0.5	1.0
3a	Ac	11AUA		10.9 ± 0.1	9.8	1.63 ± 0.01	263.7	17.5 ± 0.1	12.1
9a	Ac	11AUA-GLY		13.8 ± 0.4	7.7	1.41 ± 0.03	304.9	34.1 ± 0.1	6.2
12a	Ac	11AUA-ALA		11.6 ± 0.9	9.2	2.71 ± 0.04	158.6	30.8 ± 1.0	6.9
15a	Ac	11AUA-VAL		13.2 ± 0.2	8.1	5.4 ± 0.1	79.6	28.3 ± 0.6	7.5
3c	But	11AUA		12.74 ± 0.03	8.4	1.59 ± 0.01	270.4	35.4 ± 0.6	6.0
9c	But	11AUA-GLY		13.6 ± 0.4	7.8	1.40 ± 0.04	307.1	24 ± 0.8	8.8
12c	But	11AUA-ALA		11.2 ± 0.1	9.5	1.33 ± 0.01	323.2	27.1 ± 0.2	7.8
15c	But	11AUA-VAL		13.4 ± 0.6	7.9	1.44 ± 0.01	298.5	18.9 ± 0.5	11.2
3f	Bz	11AUA		51.6 ± 0.9	2.1	129.9 ± 2.8	3.3	83.1 ± 1.7	2.5
9f	Bz	11AUA-GLY		58.7 ± 1.6	1.8	146.4 ± 5.9	2.9	93.1 ± 0.2	2.3
12f	Bz	11AUA-ALA		20.0 ± 0.3	5.3	1.55 ± 0.01	277.4	23.5 ± 0.3	9.0
15f	Bz	11AUA-VAL		29.9 ± 1.2	3.6	2.80 ± 0.02	153.5	27.7 ± 0.1	7.6
3h	Succ	11AUA		110.8 ± 10.1	1.0	113 ± 3.5	3.8	>500	
9h	Succ	11AUA-GLY		283.5 ± 9.1	0.4	357.9 ± 1.1	1.2	>500	
12h	Succ	11AUA-ALA		278.3 ± 0.6	0.4	354.1 ± 0.6	1.2	>500	
15h	Succ	11AUA-VAL		38.7 ± 2.0	2.7	143.5 ± 8.0	3.0	125.9 ± 7.4	1.7
MA	H	H	H	36.2 ± 2.5	1.0	32.2 ± 3.8	1.0	99.2 ± 15.5	1.0
6a	Ac	Ac	11AUA	2.4 ± 0.1	15.1	3.1 ± 0.1	10.3	14.2 ± 0.1	7.0
18a	Ac	Ac	11AUA-GLY	60.2 ± 2.6	0.6	105.6 ± 3.9	0.3	66.5 ± 1.1	1.5
21a	Ac	Ac	11AUA-ALA	26.8 ± 0.3	1.4	64.5 ± 3.5	0.5	105.0 ± 3.8	0.9
24a	Ac	Ac	11AUA-VAL	68.1 ± 0.7	0.5	97.8 ± 4.9	0.3	105.6 ± 6.6	0.9
6c	But	But	11AUA	5.7 ± 0.2	6.3	1.37 ± 0.01	23.5	27.6 ± 0.4	3.6
18c	But	But	11AUA-GLY	82.8 ± 1.4	0.4	159.2 ± 4.0	0.2	70.9 ± 2.4	1.4
21c	But	But	11AUA-ALA	39.5 ± 1.0	0.9	109.1 ± 2.7	0.3	100.8 ± 6.9	1.0
24c	But	But	11AUA-VAL	243.1 ± 4.1	0.1	301.0 ± 1.5	0.1	>500	
6f	Bz	Bz	11AUA	145.0 ± 2.3	0.2	126.3 ± 4.9	0.3	>500	
18f	Bz	Bz	11AUA-GLY	159.4 ± 2.5	0.2	227.4 ± 4.0	0.1	>500	
21f	Bz	Bz	11AUA-ALA	130.8 ± 2.5	0.3	293.4 ± 0.8	0.1	>500	
24f	Bz	Bz	11AUA-VAL	104.8 ± 5.6	0.3	184.1 ± 3.0	0.2	72.1 ± 3.7	1.4
6h	Succ	Succ	11AUA	38.1 ± 1.1	1.0	153.7 ± 0.3	0.2	111.3 ± 3.1	0.9
18h	Succ	Succ	11AUA-GLY	221.1 ± 3.0	0.2	218.4 ± 5.1	0.1	344.3 ± 4.8	0.3
21h	Succ	Succ	11AUA-ALA	164.5 ± 2.6	0.2	211.6 ± 2.5	0.2	>500	
24h	Succ	Succ	11AUA-VAL	250.4 ± 1.3	0.1	212.2 ± 4.3	0.2	>500	

^aThe IC₅₀ values (μM) were calculated considering control untreated cells as 100% of viability. Cell-growth inhibition was analyzed by the MTT assay, as described in the Experimental Procedures. All assays were made two times using three replicates. Values, means ± SEM. ^bThese columns represent the ratio between the IC₅₀ of each precursor (OA or MA) and the IC₅₀ of the related derivatives.

t3 368 succinyl) on the hydroxyl groups of the A-ring of the molecules
369 (Table 3). In the cytotoxicity analysis of the OA derivatives, the
370 best results were achieved on the HT29 cell line, with the

smallest acyl groups (acetyl or butanoyl); with IC₅₀ data 371 between 1.33 and 5.4 μM , these values being between 80- and 372 323-fold lower than its precursor (OA). Also good results were 373

Table 4. Growth-Inhibitory Effects of the Monopeptidyl (GABA or 6AHA) OA or MA Acyl (ac or but) Derivatives on the Three Cancer Cell Lines

compound	R ₁	R ₂	R ₃	B16–F10 ^a	IC ₅₀ of precursor ^b /IC ₅₀ of compound	HT29 ^a	IC ₅₀ of precursor ^b /IC ₅₀ of compound	Hep G2 ^a	IC ₅₀ of precursor ^b /IC ₅₀ of compound	
OA		H	H	106.4 ± 3.7	1.0	429.9 ± 0.7	1.0	211.8 ± 0.5	1.0	
1a		Ac	GABA	81.7 ± 0.2	1.3	81.9 ± 0.3	5.3	79.9 ± 3.8	2.6	
2a		Ac	6AHA	61.4 ± 0.7	1.7	72.8 ± 1.4	5.9	75.29 ± 0.05	2.8	
1c		But	GABA	29.7 ± 1.2	3.6	45.6 ± 1.0	9.4	24.0 ± 0.9	8.8	
2c		But	6AHA	19.2 ± 0.2	5.5	20.3 ± 0.3	21.2	17.5 ± 0.1	12.1	
MA	H	H	H	36.2 ± 2.5	1.0	32.2 ± 3.8	1.0	99.2 ± 15.5	1.0	
4a		Ac	Ac	GABA	104.6 ± 1.7	0.3	95.8 ± 1.7	0.3	109.2 ± 1.5	0.9
5a		Ac	Ac	6AHA	50.2 ± 2.4	0.7	89.8 ± 0.6	0.4	87.0 ± 1.5	1.1
4c		But	But	GABA	52.3 ± 0.6	0.7	31.3 ± 0.1	1.0	18.0 ± 0.6	5.5
5c		But	But	6AHA	46.0 ± 1.5	0.8	32.1 ± 1.3	1.0	19.8 ± 0.8	5.0

^aThe IC₅₀ values (μM) were calculated considering control untreated cells as 100% of viability. Cell-growth inhibition was analyzed by the MTT assay, as described in the Experimental Procedures. All assays were made two times using three replicates. Values, means ± SEM. ^bThese columns represent the ratio between the IC₅₀ of each precursor (OA or MA) and the IC₅₀ of the related derivatives.

found with the other cell lines, with IC₅₀ data between 10.9 and 13.8 μM (B16–F10), and between 17.5 and 35.4 μM (Hep G2). The acetyl and butanoyl MA derivatives also displayed good cytotoxic activity, especially the monopeptidyl (11AUA) derivatives, with IC₅₀ data between 1.37 and 27.6 μM , these values being between 4- and 23-fold lower than its precursor (MA) (Table 3 and Charts 2).

Finally, considering the good results found using the monopeptidyl (11AUA) OA or MA derivatives with an acetyl or butanoyl group at C-2 or C-2/C-3, we also analyzed the influence of these acyl OA or MA derivatives with amino acids with a shorter chain (GABA or 6AHA). Thus, these derivatives exhibited a generally higher cytotoxicity than did their corresponding precursors (OA or MA), but lower than when the amino acid 11AUA was present (Table 4 and Charts 2).

CONCLUSIONS

In summary, we have prepared a library of 264 compounds through easy combinatorial solid-phase processes, utilizing two natural triterpene acids (OA or MA) as scaffolds. These methods have led to the semisynthesis of products with high yields and purities, and easy isolation. Several of these derivatives of OA or MA with mono- or dipeptidyl groups at C-28, and other derivatives that also included acyl groups at C-2 or C-2/C-3 of the triterpene skeleton, exhibited cytotoxic properties on B16–F10, HT29, or Hep G2 cancer cell lines. Most compounds tested displayed cytotoxicity on the B16–F10 (90%) and HT29 (90%) cell lines, while the percentage was somewhat lower (67%) for the Hep G2 cell line. Several cytotoxic OA derivatives had very low IC₅₀ values (<2 μM), being around 300-fold more effective than its precursor. Some cytotoxic MA derivatives also had low IC₅₀ values (<6 μM), in this case being between 6- and 24-fold more effective than its precursor, because MA exhibits lower IC₅₀ values than OA. Analyzing the structure–activity relationship of these OA or MA derivatives, it can be concluded that the functional groups that clearly improved the cytotoxic effects of these compounds are a long-chain ω -amino acid (11AUA) on the carboxylic group at C-28, and a small acyl group (acetyl or butanoyl) on the hydroxyl groups at C-2 or C-2/C-3 of the A-ring of the triterpene skeleton. Synthetic lipophilic compounds bearing different components are underexplored as potential therapeutic agents. The acetyl or butanoyl 11AUA-OA or -MA derivatives described here show that cytotoxic properties can

be varied in such circumstances and, therefore, may be interesting compounds for development of novel biological activity.

EXPERIMENTAL PROCEDURE

Isolation of OA and MA from Residues of Olive-Oil Industry. Oleanolic (OA) and maslinic (MA) acids were isolated from solid wastes resulting from olive-oil production, which were extracted in a Soxhlet with hexane and EtOAc successively.⁵³ Hexane extracts contained a mixture of OA and MA (80:20), whereas this relationship was (20:80) for the EtOAc extracts. Both products were purified from these mixtures by column chromatography over silica gel, eluting with a CHCl₃/MeOH or CH₂Cl₂/acetone mixtures of increasing polarity.⁵⁵

General Procedure for the Semisynthesis of Mono- or Dipeptidyl OA or MA Derivatives. The coupling of the corresponding ω -amino acids (Aa1) to the resin was the first step to form the monopeptidyl derivatives of OA or MA. Thus, an appropriate amount of CTC-resin (1.30 mmol/g) was placed in a 10 mL polypropylene syringe, fitted with a polyethylene filter disk. The resin was washed with DMF (2 mL × 3) and DCM (2 mL × 3), swelled with DCM (1 mL) for 30 min, and drained under reduced pressure. Then, a solution containing 2 equiv of the corresponding ω -Fmoc-Aa1-OH (Fmoc-GABA-OH, Fmoc-6AHA-OH or Fmoc-11AUA-OH), DIEA (10 equiv), and DCM (1.5 mL), was added, and the mixture was stirred for 1.5 h. Next, a treatment with MeOH (0.75 mL under stirring for 15 min) was performed to cap all the residual chloride in the resin, and subsequently the mixture was filtered. The corresponding Fmoc-Aa1-resin was washed with DCM (2 mL × 3) and DMF (2 mL × 3), and then the Fmoc group was removed by treatment with piperidine/DMF (1:4) (3 × 10 min). Finally, the resin was again washed with DCM (2 mL × 3) and DMF (2 mL × 3), filtered, and drained under reduced pressure.

The first step to obtain the dipeptidyl OA or MA derivatives was the coupling of the corresponding α -amino acids (Aa2) (Fmoc-GLY-OH, Fmoc-ALA-OH, or Fmoc-VAL-OH) to the resin. Thus, proceeding as described in the previous paragraph, the corresponding Aa2-resin derivatives were formed. Then, to attach the second ω -amino acid unit (Aa1), a solution with 4 equiv of the corresponding Fmoc-Aa1-OH (Fmoc-GABA-OH, Fmoc-6AHA-OH, or Fmoc-11AUA-OH), HOAt (4 equiv),

460 DIPCDI (4 equiv), in DMF, was added to the corresponding
 461 Aa2-resin contained in a syringe. The mixture was stirred for
 462 1.5 h, the ninhydrin test being negative. Finally, the
 463 corresponding Fmoc-Aa1-Aa2-resin was subjected to the
 464 above-described washing/deprotecting treatments, and then
 465 filtered and drained under reduced pressure.

466 The second step to form the mono- or dipeptidyl OA or MA
 467 derivatives was the coupling of the corresponding Aa1-resin or
 468 Aa1-Aa2-resin with one of the triterpene acids (OA or MA).
 469 Thus, a solution of OA or MA (3 equiv), PyAOP (3 equiv),
 470 HOAt (3 equiv), and DIEA (9 equiv) in DMF/DCM, was
 471 added to the syringe containing the corresponding Aa1-resin or
 472 Aa1-Aa2-resin. This mixture was stirred at rt for 24 h, the
 473 ninhydrin test proving negative. The resin coupled with the
 474 peptidyl-triterpene acid was then washed with DMF (2 mL ×
 475 3) and DCM (2 mL × 3), and drained under reduced pressure,
 476 rendering the corresponding OA- or MA-Aa1-resin derivatives,
 477 or OA- or MA-Aa1-Aa2-resin derivatives.

478 The third and final step to obtain the mono- or dipeptidyl
 479 derivatives of OA or MA (**1–24**) was the cleavage of these
 480 derivatives from the resin by treatment with DCM:TFA (99:1)
 481 (2 mL × 3 × 30 s). Then, the corresponding product was
 482 filtered, evaporated under reduced pressure, lyophilized, and
 483 the residue was analyzed by TLC and HPLC. The physical,
 484 chemical, and spectroscopic properties of representative
 485 examples are given below.

486 *N-(3β-Hydroxyolean-12-en-28-oyl)-4-aminobutanoic Acid*
 487 (**1**): HPLC retention time 4.08 min; HPLC purity 100%; white
 488 solid; mp 121–123 °C; $[\alpha]_D + 42^\circ$ (c 1, MeOH); IR
 489 $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3423, 2948, 2850, 1654; ^1H NMR (Cl_3CD)
 490 δ_{H} 6.20 (1H, t, $J = 5.1$ Hz, NH), 5.37 (1H, dd, $J = 3.0, 3.0$ Hz,
 491 H12), 3.40 (2H, dt, $J = 5.1, 7.0$ Hz, 2H–C4 GABA), 3.22 (1H,
 492 dd, $J = 5.0, 10.0$ Hz, H3), 2.52 (1H, dd, $J = 3.6, 13.7$ Hz, H18),
 493 2.35 (2H, t, $J = 7.5$ Hz, 2H–C2 GABA), 1.14, 0.96, 0.88, 0.88,
 494 0.88, 0.76, 0.73 (3H each, s, Me groups); ^{13}C NMR (Cl_3CD)
 495 δ_{C} 179.7 (C28), 176.7 (C1 GABA), 144.9 (C13), 123.3 (C12),
 496 79.3 (C3), 55.3 (C5), 47.7 (C9), 47.0 (C19), 46.6 (C17), 42.4
 497 (C18), 42.4 (C14), 39.6 (C10), 39.1 (C4 GABA), 39.0 (C8),
 498 38.7 (C1), 37.2 (C4), 34.3 (C21), 33.2 (Me), 32.7 (C7), 32.5
 499 (C22), 31.9 (C2 GABA), 30.9 (C20), 28.3 (Me), 27.5 (C2 and
 500 C15), 26.0 (Me), 25.0 (C3 GABA), 23.8 (Me and C16), 23.7
 501 (C11), 18.5 (C6), 17.1 (Me), 15.8 (Me), 15.6 (Me); ESI-
 502 HRMS (m/z) [M + Na]⁺ calcd for $\text{C}_{34}\text{H}_{55}\text{NO}_4\text{Na}$ 564.4209,
 503 found 564.4193.

504 *N-(3β-Hydroxyolean-12-en-28-oyl)-6-aminohexanoic Acid*
 505 (**2**): HPLC retention time 4.65 min; HPLC purity 100%; white
 506 solid; mp 117–119 °C; $[\alpha]_D + 68^\circ$ (c 1, MeOH); IR
 507 $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3423, 2948, 2850, 1654; ^1H NMR (Cl_3CD)
 508 δ_{H} 6.20 (1H, t, $J = 5.4$ Hz, NH), 5.37 (1H, dd, $J = 3.2, 3.2$ Hz,
 509 H12), 3.36 (2H, m, 2H–C6 6AHA), 3.26 (1H, dd, $J = 5.0, 10.0$
 510 Hz, H3), 2.44 (1H, dd, $J = 3.6, 13.7$ Hz, H18), 2.34 (2H, t, $J =$
 511 7.5 Hz, 2H–C2 6AHA), 1.14, 0.97, 0.89, 0.89, 0.87, 0.77, 0.73
 512 (3H each, s, Me groups); ^{13}C NMR (Cl_3CD) δ_{C} 180.0 (C28),
 513 178.8 (C1 6AHA), 145.0 (C13), 123.4 (C12), 79.6 (C3), 55.3
 514 (C5), 47.7 (C9), 47.0 (C19), 46.6 (C17), 42.6 (C18), 42.4
 515 (C14), 39.9 (C6 6AHA), 39.6 (C10), 38.4 (C1), 38.2 (C8),
 516 37.2 (C4), 34.3 (C21), 33.9 (C2 6AHA), 33.1 (Me), 32.4 (C7),
 517 32.3 (C22), 30.9 (C20), 29.0 (C5 6AHA and C2), 28.3 (Me),
 518 27.4 (C15), 26.6 (C4 6AHA), 25.9 (Me), 24.4 (C3 6AHA),
 519 23.9 (C11), 23.8 (C16), 23.7 (Me), 18.4 (C6), 17.1 (Me), 15.8
 520 (Me), 15.6 (Me); ESI-HRMS (m/z) [M + Na]⁺ calcd for
 521 $\text{C}_{36}\text{H}_{59}\text{NO}_4\text{Na}$ 592.4342, found 592.4353.

522 *N-(3β-Hydroxyolean-12-en-28-oyl)-11-aminoundecanoic* 523
Acid (3): HPLC retention time 11.68 min; HPLC purity 100%; 523
 524 white solid; mp 97–99 °C; $[\alpha]_D + 56^\circ$ (c 1, MeOH); IR 524
 525 $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3423, 2948, 2850, 1654; ^1H NMR (Cl_3CD) 525
 526 δ_{H} 6.10 (1H, t, $J = 5.1$ Hz, NH), 5.35 (1H, dd, $J = 3.0, 3.0$ Hz, 526
 527 H12), 3.34 (2H, m, 2H–C11 11AUA), 3.22 (1H, dd, $J = 5.0,$ 527
 528 10.0 Hz, H3), 2.45 (1H, dd, $J = 3.6, 13.7$ Hz, H18), 2.31 (2H, t, 528
 529 $J = 7.5$ Hz, 2H–C2 11AUA), 1.14, 0.97, 0.89, 0.88, 0.86, 0.76, 529
 0.74 (3H each, s, Me groups); ^{13}C NMR (Cl_3CD) δ_{C} 178.7 530
 530 (C28), 178.5 (C1 11AUA), 145.3 (C13), 123.0 (C12), 79.2 531
 531 (C3), 54.3 (C5), 47.8 (C9), 47.1 (C19), 46.5 (C17), 42.7 532
 532 (C18), 42.4 (C14), 39.9 (C11 11AUA), 39.6 (C10), 39.0 (C8), 533
 38.8 (C1), 37.2 (C4), 34.4 (C21), 34.2 (C2 11AUA), 33.2 534
 534 (Me), 32.6 (C7), 32.1 (C22), 30.9 (C20), 29.5 and 29.3 (C4, 535
 535 C5, C6, C7, C8 and C10 11AUA), 28.3 (Me), 27.5 (C15), 27.4 536
 536 (C2), 26.0 (Me), 24.9 and 24.1 (C9 11AUA and C3), 24.0 537
 537 (C16), 23.8 (Me and C11), 18.5 (C6), 17.2 (Me), 15.8 (Me), 538
 15.6 (Me); ESI-HRMS (m/z) [M + Na]⁺ calcd for 539
 539 $\text{C}_{41}\text{H}_{69}\text{NO}_4\text{Na}$ 662.5305, found 662.5308. 540

541 *N-(2α,3β-Dihydroxyolean-12-en-28-oyl)-4-aminobutanoic* 541
Acid (4): HPLC retention time 2.75 min; HPLC purity 99%; 542
 543 white solid; mp 181–183 °C; $[\alpha]_D + 17^\circ$ (c 1, MeOH); IR 543
 544 $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3432, 2947, 2899, 1711; ^1H NMR (DMSO- 544
 545 d_6) δ_{H} 7.27 (1H, t, $J = 5.1$ Hz, NH), 5.21 (1H, dd, $J = 3.0, 3.0$ 545
 546 Hz, H12), 3.39 (1H, ddd, $J = 4.3, 9.3, 12.2$ Hz, H2), 3.00 (2H, 546
 547 dt, $J = 5.1, 7.0$ Hz, 2H–C4 GABA), 2.78 (1H, dd, $J = 3.6, 13.7$ 547
 548 Hz, H18), 2.72 (1H, d, $J = 9.3$ Hz, H3), 2.16 (2H, t, $J = 7.5$ Hz, 548
 549 2H–C2 GABA), 1.06, 0.90, 0.87, 0.87, 0.85, 0.68, 0.63 (3H 549
 549 each, s, Me groups); ^{13}C NMR (DMSO- d_6) δ_{C} 176.2 (C28), 550
 174.3 (C1 GABA), 144.1 (C13), 121.3 (C12), 82.2 (C3), 67.1 551
 551 (C2), 54.7 (C5), 47.0 (C9), 46.7 (C1), 45.9 (C19), 45.2 552
 552 (C17), 41.2 (C14), 40.4 (C18), 38.8 (C10), 38.6 (C4), 38.3 553
 553 (C4 GABA), 37.6 (C8), 33.6 (C21), 32.9 (Me), 32.7 (C7), 554
 32.3 (C22), 31.2 (C2 GABA), 30.4 (C20), 28.7 (Me), 26.9 555
 555 (C15), 25.7 (Me), 24.4 (C3 GABA), 23.5 (Me), 23.0 (C16), 556
 22.1 (C11), 18.0 (C6), 17.1 (Me), 16.8 (Me), 16.3 (Me); ESI- 557
 557 HRMS (m/z) [M + Na]⁺ calcd for $\text{C}_{34}\text{H}_{55}\text{NO}_3\text{Na}$ 580.3977, 558
 558 found 580.3971. 559

560 *N-(2α,3β-Dihydroxyolean-12-en-28-oyl)-6-aminohexanoic* 560
Acid (5): HPLC retention time 3.23 min; HPLC purity 93%; 561
 561 white solid; mp 142–144 °C; $[\alpha]_D + 19^\circ$ (c 1, MeOH); IR 562
 562 $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3422, 2940, 2870, 1688; ^1H NMR (DMSO- 563
 563 d_6) δ_{H} 7.20 (1H, t, $J = 5.4$ Hz, NH), 5.20 (1H, dd, $J = 3.2, 3.2$ 564
 564 Hz, H12), 3.41 (1H, ddd, $J = 4.3, 9.3, 12.2$ Hz, H2), 2.97 (2H, 565
 565 m, 2H–C6 6AHA), 2.78 (1H, dd, $J = 3.6, 13.7$ Hz, H18), 2.72 566
 566 (1H, d, $J = 9.3$ Hz, H3), 2.16 (2H, t, $J = 7.5$ Hz, 2H–C2 567
 567 6AHA), 1.06, 0.90, 0.87, 0.86, 0.85, 0.68, 0.64 (3H each, s, Me 568
 568 groups); ^{13}C NMR (DMSO- d_6) δ_{C} 176.0 (C28), 174.3 (C1 569
 569 6AHA), 144.1 (C13), 121.2 (C12), 82.2 (C3), 67.1 (C2), 54.7 570
 570 (C5), 47.0 (C9), 46.7 (C1), 46.0 (C19), 45.1 (C17), 41.2 571
 571 (C14), 40.4 (C18), 38.9 (C10), 38.6 (C6 6AHA and C4), 37.5 572
 572 (C8), 33.6 (C2 6AHA and C21), 32.9 (Me), 32.7 (C7), 32.3 573
 573 (C22), 30.4 (C20), 28.8 (C5 6AHA), 28.7 (Me), 26.8 (C15), 574
 26.1 (C4 6AHA), 25.6 (Me), 24.2 (C3 6AHA), 23.5 (Me), 22.9 575
 575 (C16), 22.2 (C11), 18.0 (C6), 17.0 (Me), 16.8 (Me), 16.2 576
 576 (Me); ESI-HRMS (m/z) [M + Na]⁺ calcd for $\text{C}_{36}\text{H}_{59}\text{NO}_5\text{Na}$ 577
 608.4290, found 608.4295. 578

579 *N-(2α,3β-Dihydroxyolean-12-en-28-oyl)-11-aminounde-* 579
canoic Acid (6): HPLC retention time 6.78 min; HPLC purity 580
 580 100%; white solid; mp 126–128 °C; $[\alpha]_D + 2^\circ$ (c 1, MeOH); 581
 581 IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3401, 2910, 2869; ^1H NMR (DMSO- d_6) 582
 582 δ_{H} 7.19 (1H, t, $J = 5.1$ Hz, NH), 5.20 (1H, dd, $J = 3.0, 3.0$ Hz, 583
 583 H12), 3.40 (1H, ddd, $J = 4.3, 9.3, 12.2$ Hz, H2), 2.99 (2H, m, 584
 584 L dx.doi.org/10.1021/co500051z | ACS Comb. Sci. XXXX, XXX, XXX–XXX

585 2H–C11 11AUA), 2.78 (1H, dd, J = 3.6, 13.7 Hz, H18), 2.72
 586 (1H, d, J = 9.3 Hz, H3), 2.6 (2H, t, J = 7.5 Hz, 2H–C2
 587 11AUA), 1.07, 0.90, 0.88, 0.87, 0.86, 0.68, 0.65 (3H each, s, Me
 588 groups); ^{13}C NMR (DMSO- d_6) δ_{C} 175.9 (C28), 174.3 (C1
 589 11AUA), 144.1 (C13), 121.2 (C12), 82.1 (C3), 67.0 (C2), 54.7
 590 (C5), 47.0 (C9), 46.7 (C1), 46.0 (C19), 45.1 (C17), 41.2
 591 (C14), 40.2 (C18), 38.8 (C11 11AUA and C10), 38.6 (C4),
 592 37.5 (C8), 33.6 (C2 11AUA and C21), 32.9 (Me), 32.7 (C7),
 593 32.3 (C22), 30.3 (C20), 29.1 (C10 11AUA), 28.9 (C6 and C7
 594 11AUA), 28.8 (C5 and C8 11AUA), 28.7 (Me), 28.6 (C4
 595 11AUA), 26.6 (C15), 25.6 (Me), 24.5 (C3 and C9 11AUA),
 596 23.5 (Me), 22.9 (C16), 22.2 (C11), 18.0 (C6), 17.0 (Me), 16.8
 597 (Me), 16.2 (Me); ESI-HRMS (m/z) [M + Na]⁺ calcd for
 598 $\text{C}_{41}\text{H}_{69}\text{NO}_5\text{Na}$ 678.5073, found 678.5076.

599 *N’-[N-(3 β -Hydroxyolean-12-en-28-oyl)-4-aminobutanoyl]-
 600 glycine (7):* HPLC retention time 3.44 min; HPLC purity
 601 100%; white solid; mp 148–150 °C; $[\alpha]_D$ + 61° (c 1, MeOH);
 602 IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3423, 2948, 2850, 1654; ^1H NMR (Cl₃CD)
 603 δ_{H} 7.41 (1H, part X of an ABX system, J = 3.5, 5.0 Hz, NH
 604 GLY), 6.43 (1H, t, J = 3.6 Hz, NH GABA), 5.38 (1H, dd, J =
 605 3.2, 3.2 Hz, H12), 4.03 (2H, part AB of an ABX system, J = 3.5,
 606 5.0, 18.5 Hz, 2H–C2 GLY), 3.41 (2H, m, 2H–C4 GABA),
 607 3.21 (1H, dd, J = 5.0, 10.0 Hz, H3), 2.47 (1H, dd, J = 3.4, 12.5
 608 Hz, H18), 2.33 (2H, t, J = 5.4 Hz, 2H–C2 GABA), 1.14, 0.96,
 609 0.88, 0.88, 0.87, 0.76, 0.71 (3H each, s, Me groups); ^{13}C NMR
 610 (Cl₃CD) δ_{C} 180.1 (C28), 175.1 (C1 GABA), 172.4 (C1 GLY),
 611 144.6 (C13), 123.6 (C12), 79.4 (C3), 55.3 (C5), 47.7 (C9),
 612 46.9 (C19), 46.7 (C17), 42.5 (C18), 42.3 (C14), 41.9 (C2
 613 GLY), 39.6 (C10), 39.4 (C4 GABA), 39.0 (C8), 38.7 (C1),
 614 37.2 (C4), 34.2 (C21), 33.6 (C2 GABA), 33.1 (Me), 32.6
 615 (C7), 32.5 (C22), 30.9 (C20), 29.4 (C2), 28.3 (Me), 27.4
 616 (C15), 26.0 (C3 GABA and Me), 23.9 (C16), 23.7 (Me), 22.3
 617 (C11), 18.5 (C6), 17.1 (Me), 15.8 (Me), 15.5 (Me); ESI-
 618 HRMS (m/z) [M + Na]⁺ calcd for $\text{C}_{36}\text{H}_{58}\text{N}_2\text{O}_5\text{Na}$ 621.4243,
 619 found 621.4253.

620 *N’-[N-(3 β -Hydroxyolean-12-en-28-oyl)-6-aminohexano-
 621 yll-glycine (8):* HPLC retention time 3.99 min; HPLC purity
 622 100%; white solid; mp 112–114 °C; $[\alpha]_D$ + 55° (c 1, MeOH);
 623 IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3423, 2948, 2850, 1654; ^1H NMR (Cl₃CD)
 624 δ_{H} 6.86 (1H, part X of an ABX system, J = 3.3, 5.1 Hz, NH
 625 GLY), 6.20 (1H, t, J = 3.9 Hz, NH 6AHA), 5.37 (1H, dd, J =
 626 3.2, 3.2 Hz, H12), 4.02 (2H, part AB of an ABX system, J = 3.3,
 627 5.1, 18.4 Hz, 2H–C2 GLY), 3.34 (2H, m, 2H–C6 6AHA),
 628 3.22 (1H, dd, J = 5.0, 10.0 Hz, H3), 2.46 (1H, dd, J = 3.4, 12.5
 629 Hz, H18), 2.30 (2H, t, J = 5.5 Hz, 2H–C2 6AHA), 1.14, 0.96,
 630 0.89, 0.89, 0.87, 0.76, 0.72 (3H each, s, Me groups); ^{13}C NMR
 631 (Cl₃CD) δ_{C} 179.8 (C28), 174.9 (C1 6AHA), 172.5 (C1 GLY),
 632 144.9 (C13), 123.4 (C12), 79.4 (C3), 55.3 (C5), 47.7 (C9),
 633 46.9 (C19), 46.6 (C17), 42.5 (C18), 42.3 (C14), 41.8 (C2
 634 GLY), 39.7 (C6 6AHA), 39.6 (C10), 39.0 (C8), 38.7 (C1),
 635 37.2 (C4), 36.0 (C2 6AHA), 34.3 (C21), 33.1 (Me), 32.5 (C7
 636 and C22), 30.9 (C20), 29.9 (C5 6AHA), 29.0 (C2), 28.3 (Me),
 637 27.4 (C15), 26.4 (C4 6AHA), 26.1 (C3 6AHA), 25.9 (Me),
 638 23.7 (Me and C11), 23.3 (C16), 18.5 (C6), 17.1 (Me), 15.8
 639 (Me), 15.6 (Me); ESI-HRMS (m/z) [M + Na]⁺ calcd for
 640 $\text{C}_{38}\text{H}_{62}\text{N}_2\text{O}_5\text{Na}$ 649.4556, found 649.4553.

641 *N’-[N-(3 β -Hydroxyolean-12-en-28-oyl)-11-aminounde-
 642 noyl]-glycine (9):* HPLC retention time 8.07 min; HPLC purity
 643 100%; white solid; mp 110–112 °C; $[\alpha]_D$ + 57° (c 1, MeOH);
 644 IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3423, 2948, 2850, 1654; ^1H NMR (Cl₃CD)
 645 δ_{H} 6.44 (1H, part X of an ABX system, J = 3.2, 4.9 Hz, NH
 646 Gly), 6.13 (1H, t, J = 3.9 Hz, NH 11AUA), 5.36 (1H, dd, J =
 647 3.0, 3.0 Hz, H12), 4.02 (2H, part AB of an ABX system, J = 3.2,

4.9, 18.2 Hz, 2H–C2 GLY), 3.34 (2H, m, 2H–C11 11AUA), 648
 3.22 (1H, dd, J = 5.0, 10.0 Hz, H3), 2.45 (1H, dd, J = 3.6, 13.7
 649 Hz, H18), 2.25 (2H, t, J = 5.4 Hz, 2H–C2 11AUA), 1.14, 0.96,
 650 0.89, 0.89, 0.88, 0.76, 0.73 (3H each, s, Me groups); ^{13}C NMR
 651 (Cl₃CD) δ_{C} 179.5 (C28), 175.0 (C1 11AUA), 172.3 (C1 GLY),
 652 145.1 (C13), 123.3 (C12), 79.4 (C3), 55.3 (C5), 47.7 (C9),
 653 46.9 (C19), 46.6 (C17), 42.7 (C18), 42.3 (C14), 41.8 (C2 GLY),
 654 40.1 (C11 11AUA), 39.6 (C10), 39.0 (C8), 38.7 (C1), 37.2 (C4),
 655 36.4 (C2 11AUA), 34.3 (C21), 33.1 (Me), 32.4 (C7 and C22),
 656 30.9 (C20), 29.4 (C2), 29.3, 29.2, and 28.9 (C4, C5, C6, C7,
 657 C8 and C10 11AUA), 28.3 (Me), 27.4 (C15), 25.9 (Me), 25.8 and
 658 25.1 (C3 and C9 11AUA), 23.7 (Me), 23.3 (C11), 22.9 (C16),
 659 18.5 (C6), 17.1 (Me), 15.8 (Me), 15.6 (Me); ESI-HRMS
 660 (m/z) [M + Na]⁺ calcd for $\text{C}_{43}\text{H}_{72}\text{N}_2\text{O}_5\text{Na}$ 661
 719.5339, found 719.5336. 662

663 *N’-[N-(3 β -Hydroxyolean-12-en-28-oyl)-4-aminobutanoyl]-
 664 L-alanine (10):* HPLC retention time 3.39 min; HPLC purity
 665 100%; white solid; mp 140–142 °C; $[\alpha]_D$ + 54° (c 1, MeOH);
 666 IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3423, 2948, 2850, 1654; ^1H NMR (Cl₃CD)
 667 δ_{H} 7.35 (1H, d, J = 5.4 Hz, NH ALA), 6.41 (1H, t, J = 5.8 Hz,
 668 NH GABA), 5.37 (1H, dd, J = 3.2, 3.2 Hz, H12), 4.53 (1H, dq,
 669 J = 5.4, 5.4 Hz, 1H–C2 ALA), 3.37 (2H, m, 2H–C4 GABA),
 670 3.22 (1H, dd, J = 5.0, 10.0 Hz, H3), 2.48 (1H, dd, J = 3.4, 12.5
 671 Hz, H18), 2.31 (2H, t, J = 5.1 Hz, 2H–C2 GABA), 1.43 (3H,
 672 d, J = 5.4 Hz, 3H–C3 ALA), 1.13, 0.96, 0.88, 0.88, 0.87, 0.75,
 673 0.71 (3H each, s, Me groups); ^{13}C NMR (Cl₃CD) δ_{C} 180.3 (C28),
 674 175.1 (C1 GABA), 174.0 (C1 ALA), 144.6 (C13), 123.4 (C12),
 675 79.3 (C3), 55.3 (C5), 48.7 (C2 ALA), 47.7 (C9), 46.9 (C19),
 676 46.6 (C17), 42.5 (C18), 42.2 (C14), 39.6 (C10), 39.3 (C4 GABA),
 677 38.9 (C8), 38.7 (C1), 37.2 (C4), 34.2 (C21), 33.7 (C2 GABA),
 678 33.1 (Me), 32.6 (C7), 32.5 (C22), 30.9 (C20), 29.4 (C2),
 679 28.3 (Me), 27.4 (C15), 26.0 (Me), 25.9 (C3 GABA), 23.9 (C16),
 680 23.7 (Me and C11), 18.5 (C6), 18.3 (Me ALA), 17.1 (Me),
 681 15.8 (Me), 15.6 (Me); ESI-HRMS (m/z) [M + Na]⁺ calcd for
 682 $\text{C}_{37}\text{H}_{60}\text{N}_2\text{O}_5\text{Na}$ 635.4400, found 635.4416. 683

683 *N’-[N-(3 β -Hydroxyolean-12-en-28-oyl)-6-aminohexano-
 684 yll-L-alanine (11):* HPLC retention time 3.92 min; HPLC
 685 purity 100%; white solid; mp 120–122 °C; $[\alpha]_D$ + 49° (c 1, MeOH);
 686 IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3423, 2948, 2850, 1654; ^1H NMR
 687 (Cl₃CD) δ_{H} 6.98 (1H, d, J = 5.1 Hz, NH ALA), 6.24 (1H, t, J =
 688 3.9 Hz, NH 6AHA), 5.37 (1H, dd, J = 3.2, 3.2 Hz, H12), 4.56 (1H,
 689 dq, J = 5.1, 5.1 Hz, 1H–C2 ALA), 3.34 (2H, m, 2H–C6 6AHA),
 690 3.23 (1H, dd, J = 5.0, 10.0 Hz, H3), 2.44 (1H, dd, J = 690
 3.4, 12.5 Hz, H18), 2.26 (2H, t, J = 5.4 Hz, 2H–C2 6AHA),
 691 1.41 (3H, d, J = 5.1 Hz, 3H–C3 ALA), 1.13, 0.96, 0.88, 0.88,
 692 0.87, 0.76, 0.72 (3H each, s, Me groups); ^{13}C NMR (Cl₃CD)
 693 δ_{C} 180.0 (C28), 175.3 (C1 6AHA), 174.6 (C1 ALA), 144.8 (C13),
 694 123.4 (C12), 79.5 (C3), 55.3 (C5), 48.5 (C2 ALA), 47.7 (C9),
 695 46.9 (C19), 46.6 (C17), 42.3 (C14 and C18), 39.8 (C6 6AHA),
 696 39.6 (C10), 38.9 (C8), 38.7 (C1), 37.1 (C4), 36.0 (C2 6AHA),
 697 34.2 (C21), 33.1 (Me), 32.5 (C7), 32.4 (C22), 30.8 (C20),
 698 29.9 (C2), 29.8 (C5 6AHA), 28.3 (Me), 27.4 (C15), 27.1 (C4 6AHA),
 699 26.4 (C3 6AHA), 25.9 (Me), 23.9 (C16), 23.7 (Me and C11),
 700 18.5 (C6), 18.2 (Me ALA), 17.1 (Me), 15.8 (Me), 15.6 (Me);
 701 ESI-HRMS (m/z) [M + Na]⁺ calcd for $\text{C}_{39}\text{H}_{64}\text{N}_2\text{O}_5\text{Na}$ 663.4713, found 663.4720. 702

703 *N’-[N-(3 β -Hydroxyolean-12-en-28-oyl)-11-aminounde-
 704 noyl-L-alanine (12):* HPLC retention time 8.67 min; HPLC
 705 purity 100%; white solid; mp 115–117 °C; $[\alpha]_D$ + 40° (c 1, MeOH);
 706 IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3423, 2948, 2850, 1654; ^1H NMR
 707 (Cl₃CD) δ_{H} 6.49 (1H, d, J = 5.7 Hz, NH ALA), 6.14 (1H, t, J =
 708 3.6 Hz, NH 11AUA), 5.36 (1H, dd, J = 3.0, 3.0 Hz, H12), 4.55 (1H,
 709 dq, J = 5.7, 5.7 Hz, 1H–C2 ALA), 3.30 (2H, m, 2H–C11

711 11AUA), 3.23 (1H, dd, $J = 5.0, 10.0$ Hz, H3), 2.45 (1H, dd, $J =$
 712 3.6, 13.7 Hz, H18), 2.23 (2H, t, $J = 5.7$ Hz, 2H–C2 11AUA),
 713 1.42 (3H, d, $J = 5.7$ Hz, 3H–C3 ALA), 1.13, 0.96, 0.89, 0.89,
 714 0.87, 0.76, 0.73 (3H each, s, Me groups); ^{13}C NMR (Cl_3CD)
 715 δ_{C} 179.6 (C28), 175.1 (C1 11AUA), 174.5 (C1 ALA), 145.1
 716 (C13), 123.3 (C12), 79.5 (C3), 55.3 (C5), 48.5 (C2 ALA),
 717 47.7 (C9), 47.0 (C19), 46.6 (C17), 42.7 (C18), 42.3 (C14),
 718 40.1 (C11 11AUA), 39.6 (C10), 39.0 (C8), 38.7 (C1), 37.2
 719 (C4), 36.5 (C2 11AUA), 34.3 (C21), 33.1 (Me), 32.5 (C7),
 720 32.4 (C22), 30.9 (C20), 29.5 (C2), 29.9, 29.4, 29.2, and 29.1
 721 (C4, C5, C6, C7, C8 and C10 11AUA), 28.3 (Me), 27.4 (C15),
 722 25.9 (Me), 25.8 (C3 and C9 11AUA), 23.9 (C16), 23.8 (C11),
 723 23.7 (Me), 18.5 (C6), 18.2 (Me ALA), 17.1 (Me), 15.6 (2 Me);
 724 ESI-HRMS (m/z) [M + Na]⁺ calcd for $\text{C}_{44}\text{H}_{74}\text{N}_2\text{O}_5\text{Na}$
 725 733.5495, found 733.5495.

726 *N’-[N-(3 β -Hydroxyolean-12-en-28-oyl)-4-aminobutanoyl]-
 727 L-valine (13)*: HPLC retention time 4.71 min; HPLC purity
 728 100%; white solid; mp 105–107 °C; $[\alpha]_D + 60^\circ$ (c 1, MeOH);
 729 IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3423, 2948, 2850, 1654; ^1H NMR (Cl_3CD)
 730 δ_{H} 7.35 (1H, d, $J = 6.3$ Hz, NH VAL), 6.43 (1H, t, $J = 3.9$ Hz,
 731 NH GABA), 5.38 (1H, dd, $J = 3.2, 3.2$ Hz, H12), 4.54 (1H, dd,
 732 J = 4.5, 6.3 Hz, 1H–C2 VAL), 3.34 (2H, m, 2H–C4 GABA),
 733 3.22 (1H, dd, $J = 5.0, 10.0$ Hz, H3), 2.45 (1H, dd, $J = 3.4, 12.5$
 734 Hz, H18), 2.40–2.10 (2H, m, 1H–C3 VAL and 1H–C2
 735 GABA), 0.93 (6H, d, $J = 4.5$ Hz, 3H–C4 and 3H–C5 VAL),
 736 1.13, 0.96, 0.88, 0.87, 0.76, 0.71 (3H each, s, Me groups);
 737 ^{13}C NMR (Cl_3CD) δ_{C} 180.3 (C28), 174.7 (C1 GABA), 174.1
 738 (C1 VAL), 144.5 (C13), 123.5 (C12), 79.4 (C3), 57.6 (C2
 739 VAL), 55.3 (C5), 47.7 (C9), 46.9 (C19), 46.7 (C17), 42.3
 740 (C14), 42.2 (C18), 39.6 (C10), 39.5 (C4 GABA), 38.9 (C8),
 741 38.7 (C1), 37.2 (C4), 34.2 (C21), 34.0 (C2 GABA), 33.1
 742 (Me), 32.6 (C7), 32.5 (C22), 31.4 (C3 VAL), 30.9 (C20), 29.9
 743 (C2), 28.3 (Me), 27.4 (C15), 26.2 (C3 GABA), 26.0 (Me),
 744 23.8 (C16), 23.7 (Me and C11), 19.1 (Me VAL), 18.4 (C6),
 745 18.0 (Me Val), 17.2 (Me), 15.8 (Me), 15.5 (Me); ESI-HRMS
 746 (m/z) [M + Na]⁺ calcd for $\text{C}_{39}\text{H}_{64}\text{N}_2\text{O}_5\text{Na}$ 663.4713, found
 747 663.4725.

748 *N’-[N-(3 β -Hydroxyolean-12-en-28-oyl)-6-aminohexano-
 749 yl]-L-valine (14)*: HPLC retention time 5.27 min; HPLC purity
 750 100%; white solid; mp 90–92 °C; $[\alpha]_D + 51^\circ$ (c 1, MeOH); IR
 751 $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3423, 2948, 2850, 1654; ^1H NMR (Cl_3CD):
 752 δ_{H} 6.84 (1H, d, $J = 6.3$ Hz, NH VAL), 6.21 (1H, t, $J = 3.9$ Hz,
 753 NH 6AHA), 5.37 (1H, dd, $J = 3.2, 3.2$ Hz, H12), 4.57 (1H, dd,
 754 J = 4.5, 6.3 Hz, 1H–C2 VAL), 3.34 (2H, m, 2H–C6 6AHA),
 755 3.22 (1H, dd, $J = 5.0, 10.0$ Hz, H3), 2.45 (1H, dd, $J = 3.4, 12.5$
 756 Hz, H18), 2.40–2.10 (2H, m, 1H–C3 VAL and 1H–C2
 757 6AHA), 0.94 (6H, d, $J = 4.5$ Hz, 3H–C4 and 3H–C5 VAL),
 758 1.14, 0.96, 0.89, 0.87, 0.76, 0.72 (3H each, s, Me groups);
 759 ^{13}C NMR (Cl_3CD) δ_{C} 179.8 (C28), 174.8 (C1 6AHA), 174.4
 760 (C1 VAL), 144.9 (C13), 123.4 (C12), 79.4 (C3), 57.5 (C2
 761 VAL), 55.3 (C5), 47.7 (C9), 47.0 (C19), 46.6 (C17), 42.5
 762 (C18), 42.3 (C14), 39.7 (C6 6AHA), 39.6 (C10), 38.9 (C8),
 763 38.7 (C1), 37.2 (C4), 36.1 (C2 6AHA), 34.2 (C21), 33.1 (Me),
 764 32.5 (C7), 32.4 (C22), 31.2 (C3 VAL), 30.9 (C20), 29.9 (C5
 765 6AHA), 28.9 (C2), 28.8 (Me), 27.4 (C15), 26.3 (C4 6AHA),
 766 26.1 (C3 6AHA), 25.9 (Me), 23.8 (C16), 23.7 (Me and C11),
 767 19.3 (Me VAL), 18.5 (C6), 18.0 (Me VAL), 17.1 (Me), 15.8
 768 (Me), 15.6 (Me); ESI-HRMS (m/z) [M + Na]⁺ calcd for
 769 $\text{C}_{41}\text{H}_{68}\text{N}_2\text{O}_5\text{Na}$ 691.5026, found 691.5815.

770 *N’-[N-(3 β -Hydroxyolean-12-en-28-oyl)-4-aminounde-
 771 noyl]-L-valine (15)*: HPLC retention time 9.48 min; HPLC
 772 purity 100%; white solid; mp 93–95 °C; $[\alpha]_D + 48^\circ$ (c 1,
 773 MeOH); IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3423, 2948, 2850, 1654; ^1H NMR

(Cl_3CD) δ_{H} 6.29 (1H, d, $J = 6.0$ Hz, NH VAL), 6.11 (1H, t, $J =$
 774 3.9 Hz, NH 11AUA), 5.34 (1H, dd, $J = 3.2, 3.2$ Hz, H12), 4.55 775
 (1H, dd, $J = 4.5, 6.0$ Hz, 1H–C2 VAL), 3.32 (2H, m, 2H–C11 776
 11AUA), 3.22 (1H, dd, $J = 5.0, 10.0$ Hz, H3), 2.46 (1H, dd, $J =$
 777 3.4, 12.5 Hz, H18), 2.40–2.10 (2H, m, 1H–C3 VAL and 1H–
 778 C2 11AUA), 0.93 (6H, d, $J = 4.5$ Hz, 3H–C4 and 3H–C5 779
 VAL), 1.13, 0.95, 0.90, 0.89, 0.85, 0.76, 0.73 (3H each, s, Me 780
 groups); ^{13}C NMR (Cl_3CD) δ_{C} 179.4 (C28), 174.5 (C1 781
 11AUA), 174.2 (C1 VAL), 145.1 (C13), 123.2 (C12), 79.4 782
 (C3), 57.3 (C2 VAL), 55.3 (C5), 47.7 (C9), 38.7 (C1), 47.0 783
 (C19), 46.5 (C17), 42.3 (C14), 42.6 (C18), 39.6 (C10), 37.2 784
 (C4), 40.0 (C11 11AUA), 39.0 (C8), 36.8 (C2 11AUA), 34.3 785
 (C21), 33.1 (Me), 32.5 (C7), 32.4 (C22), 31.3 (C3 Val), 30.9 786
 (C20), 29.9, 29.5, 29.4, 29.3, and 29.2 (C4, C5, C6, C7, C8 and 787
 C10 11AUA), 29.4 (C2), 28.3 (Me), 27.4 (C15), 25.9 (C9 and 788
 C3 11AUA, and Me), 23.9 (C16), 23.7 (C11), 23.2 (Me), 19.2 789
 (Me VAL), 18.5 (C6), 17.9 (Me Val), 17.1 (Me), 15.8 (Me), 790
 15.6 (Me); ESI-HRMS (m/z) [M + Na]⁺ calcd for 791
 $\text{C}_{46}\text{H}_{78}\text{N}_2\text{O}_5\text{Na}$ 761.5808, found 761.5815. 792

793 *N’-[N-(2 α ,3 β -Dihydroxyolean-12-en-28-oyl)-4-aminobuta-
 794 noyl]-glycine (16)*: HPLC retention time 2.35 min; HPLC 794
 purity 100%; white solid; mp 157–159 °C; $[\alpha]_D + 8^\circ$ (c 1, 795
 MeOH); IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3389, 2930, 2891, 1700; ^1H NMR 796
 ($\text{DMSO}-d_6$) δ_{H} 8.01 (1H, part X of an ABX system, $J = 3.4, 5.0$ 797
 Hz, NH GLY); 7.23 (1H, t, $J = 3.6$ Hz, NH GABA); 5.20 (1H, 798
 dd, $J = 3.2, 3.2$ Hz, H12), 3.71 (2H, part AB of an ABX system, 799
 $J = 3.4, 5.0, 18.5$ Hz, 2H–C2 GLY), 3.41 (1H, ddd, $J = 4.3, 800$
 10.5, 12.2 Hz, H2), 2.98 (2H, m, 2H–C4 GABA), 2.77 (1H, 801
 dd, $J = 3.4, 12.5$ Hz, H18), 2.73 (1H, d, $J = 10.5$ Hz, H3), 2.08 802
 (2H, t, $J = 5.4$ Hz, 2H–C2 GABA), 1.07, 0.90, 0.88, 0.87, 0.85, 803
 0.68, 0.63 (3H each, s, Me groups); ^{13}C NMR ($\text{DMSO}-d_6$) δ_{C} 804
 176.2 (C28), 172.4 (C1 GABA), 171.3 (C1 GLY), 144.1 805
 (C13), 121.3 (C12), 82.3 (C3), 67.2 (C2), 54.8 (C5), 47.1 806
 (C9), 46.8 (C1), 46.0 (C19), 45.2 (C17), 41.3 (C14), 40.5 (C2 807
 GLY), 40.4 (C18), 38.9 (C4 GABA and C10), 38.6 (C4), 37.6 808
 (C8), 33.6 (C21), 32.9 (Me), 32.8 (C7), 32.7 (C2 GABA), 809
 32.3 (C22), 30.4 (C20), 28.8 (Me), 26.9 (C15), 25.7 (Me), 810
 25.2 (C3 GABA), 23.6 (Me), 23.0 (C16), 22.2 (C11), 18.0 811
 (C6), 17.1 (Me), 16.8 (Me), 16.3 (Me); ESI-HRMS (m/z) [M 812
 + Na]⁺ calcd for $\text{C}_{36}\text{H}_{58}\text{N}_2\text{O}_6\text{Na}$ 637.4192, found 637.4197. 813

814 *N’-[N-(2 α ,3 β -Dihydroxyolean-12-en-28-oyl)-6-aminohex-
 815 anoyl]-glycine (17)*: HPLC retention time 4.71 min; HPLC 815
 purity of 100%; white solid; mp 145–147 °C; $[\alpha]_D + 2^\circ$ (c 1, 816
 MeOH); IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3423, 2942, 2890, 1678; ^1H NMR 817
 ($\text{DMSO}-d_6$) δ_{H} 8.04 (1H, part X of an ABX system, $J = 3.3, 5.0$ 818
 Hz, NH GLY), 7.15 (1H, t, $J = 3.9$ Hz, NH 6AHA), 5.20 (1H, 819
 dd, $J = 3.2, 3.2$ Hz, H12), 3.70 (2H, part AB of an ABX system, 820
 $J = 3.3, 5.0, 18.4$ Hz, 2H–C2 GLY), 3.41 (1H, ddd, $J = 4.3, 821$
 10.5, 12.2 Hz, H2), 2.96 (2H, m, 2H–C6 6AHA), 2.77 (1H, 822
 dd, $J = 3.4, 12.5$ Hz, H18), 2.73 (1H, d, $J = 10.5$ Hz, H3), 2.10 823
 (2H, t, $J = 5.5$ Hz, 2H–C2 6AHA), 1.07, 0.90, 0.87, 0.86, 0.85, 824
 0.69, 0.64 (3H each, s, Me groups); ^{13}C NMR ($\text{DMSO}-d_6$) δ_{C} 825
 176.0 (C28), 172.6 (C1 6AHA), 171.4 (C1 GLY), 144.2 826
 (C13), 121.3 (C12), 82.3 (C3), 67.1 (C2), 54.8 (C5), 47.1 827
 (C9), 46.8 (C1), 46.0 (C19), 45.2 (C17), 41.3 (C14 and C18), 828
 39.1 (C10), 38.9 (C2 GLY and C4), 38.7 (C6 6AHA), 37.6 829
 (C8), 35.0 (C2 6AHA), 33.7 (C21), 32.9 (Me), 32.7 (C7), 32.4 830
 (C22), 30.4 (C20), 28.9 (C5 6AHA), 28.8 (Me), 26.6 (C15), 831
 26.2 (C4 6AHA), 25.7 (Me), 24.9 (C3 6AHA), 23.6 (Me), 23.0 832
 (C16), 22.2 (C11), 18.0 (C6), 17.1 (Me), 16.8 (Me), 16.3 833
 (Me); ESI-HRMS (m/z) [M + Na]⁺ calcd for $\text{C}_{38}\text{H}_{62}\text{N}_2\text{O}_6\text{Na}$ 834
 665.4506, found 665.4496. 835

836 *N'-(N-(2 α ,3 β -Dihydroxyolean-12-en-28-oyl)-11-aminoun-*
 837 *decanoyl]-glycine (18)*: HPLC retention time 4.80 min; HPLC
 838 purity 100%; white solid; mp 134–136 °C; $[\alpha]_D + 26^\circ$ (c 1,
 839 MeOH); IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3399, 2968, 2901, 1699; ^1H NMR
 840 (DMSO- d_6) δ_{H} 8.03 (1H, part X of an ABX system, $J = 3.2, 4.9$
 841 Hz, NH GLY), 7.15 (1H, t, $J = 3.9$ Hz, NH 11AUA), 5.20 (1H,
 842 dd, $J = 3.0, 3.0$ Hz, H12), 3.69 (2H, part AB of an ABX system,
 843 $J = 3.2, 4.9, 18.2$ Hz, 2H–C2 GLY), 3.40 (1H, ddd, $J = 4.3, 9.3,$
 844 12.2 Hz, H2), 2.97 (2H, m, 2H–C11 11AUA), 2.78 (1H, dd, J
 845 = 3.6, 13.7 Hz, H18), 2.72 (1H, d, $J = 9.3$ Hz, H3), 2.06 (2H, t,
 846 $J = 5.4$ Hz, 2H–C2 11AUA), 1.07, 0.90, 0.87, 0.86, 0.84, 0.68,
 847 0.64 (3H each, s, Me groups); ^{13}C NMR (DMSO- d_6) δ_{C} 176.0
 848 (C28), 172.5 (C1 11AUA), 171.4 (C1 GLY), 144.3 (C13),
 849 121.2 (C12), 82.2 (C3), 67.1 (C2), 55.7 (C5), 47.1 (C9), 46.8
 850 (C1), 46.0 (C19), 45.2 (C17), 41.3 (C14), 40.9 (C18), 39.1
 851 (C10), 38.9 (C4), 38.7 (C11 11AUA and C2 GLY), 37.6 (C8),
 852 35.1 (C2 11AUA), 33.7 (C21), 32.9 (Me), 32.7 (C7), 32.4
 853 (C22), 30.4 (C20), 29.1 (C10 11AUA), 28.9 (C5,C6, C7, and
 854 C8 11AUA), 28.6 (C4 11AUA and Me), 26.6 (C15), 25.9
 855 (Me), 25.2 (C3 and C9 11AUA), 23.6 (Me), 23.0 (C16), 22.3
 856 (C11), 18.0 (C6), 17.1 (Me), 16.9 (Me), 16.3 (Me); ESI-
 857 HRMS (m/z) [M + Na]⁺ calcd for C₄₃H₇₂N₂O₆Na 735.5280,
 858 found 735.5284.

859 *N'-(N-(2 α ,3 β -Dihydroxyolean-12-en-28-oyl)-4-aminobuta-*
 860 *noyl]-L-alanine (19)*: HPLC retention time 2.59 min; HPLC
 861 purity 100%; white solid; mp 148–150 °C; $[\alpha]_D + 3^\circ$ (c 1,
 862 MeOH); IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3411, 2935, 2887, 1715; ^1H NMR
 863 (DMSO- d_6) δ_{H} 8.06 (1H, d, $J = 5.4$ Hz, NH ALA), 7.23 (1H, t,
 864 $J = 5.8$ Hz, NH GABA), 5.20 (1H, dd, $J = 3.2, 3.2$ Hz, H12),
 865 4.17 (1H, dq, $J = 5.4, 5.4$ Hz, 1H–C2 ALA), 3.41 (1H, ddd, $J =$
 866 4.3, 10.5, 12.2 Hz, H2), 2.97 (2H, m, 2H–C4 GABA), 2.77
 867 (1H, dd, $J = 3.4, 12.5$ Hz, H18), 2.73 (1H, d, $J = 10.5$ Hz, H3),
 868 2.06 (2H, t, $J = 5.1$ Hz, 2H–C2 GABA), 1.23 (3H, d, $J = 5.4$
 869 Hz, 3H–C3 ALA), 1.06, 0.90, 0.87, 0.86, 0.84, 0.68, 0.63 (3H
 870 each, s, Me groups); ^{13}C NMR (DMSO- d_6) δ_{C} 176.2 (C28),
 871 174.2 (C1 GABA), 171.8 (C1 ALA), 144.1 (C13), 121.3
 872 (C12), 82.2 (C3), 67.1 (C2), 54.8 (C5), 47.3 (C2 ALA), 47.1
 873 (C9), 46.8 (C1), 46.0 (C19), 45.2 (C17), 41.2 (C14), 40.7
 874 (C18), 38.9 (C10), 38.7 (C4), 38.6 (C4 GABA), 37.6 (C8),
 875 32.9 (C21), 32.8 (Me), 32.7 (C7 and C22), 32.3 (C2 GABA),
 876 30.4 (C20), 28.8 (Me), 26.9 (C15), 25.7 (Me), 25.1 (C3
 877 GABA), 23.6 (Me), 23.0 (C16), 22.2 (C11), 18.0 (C6), 17.0
 878 (Me ALA), 17.1 (Me), 16.8 (Me), 16.2 (Me); ESI-HRMS ($m/$
 879 z) [M + Na]⁺ calcd for C₃₇H₆₀N₂O₆Na 651.4349, found
 880 651.4350.

881 *N'-(N-(2 α ,3 β -Dihydroxyolean-12-en-28-oyl)-6-aminohex-*
 882 *anoyl]-L-alanine (20)*: HPLC retention time 3.25 min; HPLC
 883 purity 100%; white solid; mp 146–148 °C; $[\alpha]_D + 5^\circ$ (c 1,
 884 MeOH); IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3412, 2943, 2888, 1720; ^1H NMR
 885 (DMSO- d_6) δ_{H} 8.00 (1H, d, $J = 5.1$ Hz, NH ALA), 7.16 (1H, t,
 886 $J = 3.9$ Hz, NH 6AHA), 5.20 (1H, dd, $J = 3.2, 3.2$ Hz, H12),
 887 4.18 (1H, dq, $J = 5.1, 5.1$ Hz, 1H–C2 ALA), 3.41 (1H, ddd, $J =$
 888 4.3, 10.5, 12.2 Hz, H2), 2.97 (2H, m, 2H–C6 6AHA), 2.77
 889 (1H, dd, $J = 3.4, 12.5$ Hz, H18), 2.73 (1H, d, $J = 10.5$ Hz, H3),
 890 2.06 (2H, t, $J = 5.4$ Hz, 2H–C2 6AHA), 1.22 (3H, d, $J = 5.1$
 891 Hz, 3H–C3 ALA), 1.06, 0.90, 0.87, 0.86, 0.84, 0.69, 0.64 (3H
 892 each, s, Me groups); ^{13}C NMR (DMSO- d_6) δ_{C} 176.0 (C28),
 893 174.2 (C1 6AHA), 171.9 (C1 ALA), 144.2 (C13), 121.3 (C12),
 894 82.2 (C3), 67.1 (C2), 54.8 (C5), 47.3 (C2 ALA), 47.1 (C9),
 895 46.8 (C1), 46.1 (C19), 45.1 (C17), 41.3 (C14), 41.1 (C18),
 896 39.1 (C10), 38.9 (C4), 38.7 (C6 6AHA), 37.6 (C8), 35.0 (C2
 897 6AHA), 33.7 (C21), 32.9 (Me), 32.8 (C7), 32.4 (C22), 30.4
 898 (C20), 28.9 (C5 6AHA), 28.8 (Me), 26.9 (C15), 26.2 (C4

6AHA), 25.7 (Me), 24.9 (C3 6AHA), 23.6 (Me), 23.0 (C16), 899
 22.3 (C11), 18.0 (C6), 17.2 (Me ALA), 17.1 (Me), 16.8 (Me), 900
 16.3 (Me); ESI-HRMS (m/z) [M + Na]⁺ calcd for 901
 C₃₉H₆₄N₂O₆Na 679.4662, found 679.4671. 902

903 *N'-(N-(2 α ,3 β -Dihydroxyolean-12-en-28-oyl)-11-aminoun-*
 904 *decanoyl]-L-alanine (21)*: HPLC retention time 5.79 min; 904
 905 HPLC purity 100%; white solid; mp 140–142 °C; $[\alpha]_D + 17^\circ$ 905
 906 (c 1, MeOH); IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3423, 2911, 2869, 1728; ^1H 906
 907 NMR (DMSO- d_6) δ_{H} 7.99 (1H, d, $J = 5.7$ Hz, NH ALA), 7.15 907
 908 (1H, t, $J = 3.6$ Hz, NH 11AUA), 5.20 (1H, dd, $J = 3.0, 3.0$ Hz, 908
 909 H12), 4.19 (1H, dq, $J = 5.7, 5.7$ Hz, 1H–C2 ALA), 3.40 (1H, 909
 910 ddd, $J = 4.3, 9.3, 12.2$ Hz, H2), 2.97 (2H, m, 2H–C11 11AUA), 910
 911 2.78 (1H, dd, $J = 3.6, 13.7$ Hz, H18), 2.72 (1H, d, $J = 9.3$ Hz, 911
 912 H3), 2.06 (2H, t, $J = 5.7$ Hz, 2H–C2 11AUA), 1.22 (3H, d, $J =$ 912
 913 5.7 Hz, 3H C3 ALA), 1.07, 0.90, 0.88, 0.87, 0.85, 0.68, 0.65 (3H 913
 914 each, s, Me groups); ^{13}C NMR (DMSO- d_6): δ_{C} 176.0 (C28), 914
 915 174.2 (C1 11AUA), 171.9 (C1 ALA), 144.2 (C13), 121.2 915
 916 (C12), 82.2 (C3), 67.1 (C2), 54.8 (C5), 47.4 (C2 ALA), 47.3 916
 917 (C9), 46.9 (C1), 46.1 (C19), 45.2 (C17), 41.3 (C14), 40.9 917
 918 (C18), 39.2 (C10), 39.1 (C4), 38.9 (C11 11AUA), 37.6 (C8), 918
 919 35.1 (C2 11AUA), 33.7 (C21), 33.0 (Me), 32.7 (C7), 32.4 919
 920 (C22), 30.4 (C20), 29.1 (C10 11AUA), 29.0 (C6 and C7 920
 921 11AUA), 28.9 (C5 and C8 11AUA), 28.8 (Me), 28.7 (C4 921
 922 11AUA), 27.0 (C9 11AUA and C15), 26.7 (C3 11AUA), 25.7 922
 923 (Me), 23.6 (Me), 23.1 (C16), 22.3 (C11), 18.1 (C6), 17.2 (Me 923
 924 ALA), 17.1 (Me), 16.9 (Me), 16.3 (Me); ESI-HRMS m/z [M + 924
 925 Na]⁺ calcd for C₄₄H₇₄N₂O₆Na 749.5444, found 749.5440. 925

926 *N'-(N-(2 α ,3 β -Dihydroxyolean-12-en-28-oyl)-4-aminobuta-*
 927 *noyl]-L-valine (22)*. HPLC retention time 3.00 min; HPLC 927
 928 purity 100%; white solid; mp 171–173 °C; $[\alpha]_D + 29^\circ$ (c 1, 928
 929 MeOH); IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3400, 2939, 2880, 1678; ^1H NMR 929
 930 (DMSO- d_6) δ_{H} 7.92 (1H, d, $J = 6.3$ Hz, NH VAL), 7.24 (1H, t, 930
 931 $J = 3.9$ Hz, NH GABA), 5.20 (1H, dd, $J = 3.2, 3.2$ Hz, H12), 931
 932 4.14 (1H, dd, $J = 4.5, 6.3$ Hz, 1H–C2 VAL), 3.41 (1H, ddd, $J =$ 932
 933 4.3, 10.5, 12.2 Hz, H2), 3.00 (2H, m, 2H–C4 GABA), 2.77 933
 934 (1H, dd, $J = 3.4, 12.5$ Hz, H18), 2.73 (1H, d, $J = 10.5$ Hz, H3), 934
 935 2.10–1.98 (2H, m, 1H–C3 VAL and 1H–C2 GABA), 0.86 935
 936 (6H, d, $J = 4.5$ Hz, 3H–C4 and 3H–C5 VAL), 1.07, 0.90, 0.88, 936
 937 0.86, 0.85, 0.68, 0.63 (3H each, s, Me groups); ^{13}C NMR 937
 938 (DMSO- d_6) δ_{C} 176.2 (C28), 173.1 (C1 GABA), 172.3 (C1 938
 939 VAL), 144.1 (C13), 121.3 (C12), 82.2 (C3), 67.1 (C2), 57.0 939
 940 (C2 VAL), 54.7 (C5), 47.3 (C9), 47.1 (C1), 46.2 (C19), 45.2 940
 941 (C17), 41.2 (C14), 40.9 (C18), 39.3 (C10), 39.0 (C4 GABA), 941
 942 38.9 (C4), 37.6 (C8), 33.6 (C21), 32.9 (Me), 32.8 (C7), 32.7 942
 943 (C22), 32.3 (C2 GABA), 30.4 (C20), 29.8 (C3 VAL), 28.8 943
 944 (Me), 26.9 (C15), 25.7 (Me), 25.5 (C3 GABA), 23.5 (Me), 944
 945 23.0 (C16), 22.2 (C11), 19.1 (2 Me VAL), 18.0 (C6), 17.1 945
 946 (Me), 16.9 (Me), 16.3 (Me); ESI-HRMS (m/z) [M + Na]⁺ 946
 947 calcd for C₃₉H₆₄N₂O₆Na 679.4662, found 679.4666. 947

948 *N'-(N-(2 α ,3 β -Dihydroxyolean-12-en-28-oyl)-6-aminohex-*
 949 *anoyl]-L-valine (23)*: HPLC retention time 4.46 min; HPLC 949
 950 purity 100%; white solid; mp 160–162 °C; $[\alpha]_D + 27^\circ$ (c 1, 950
 951 MeOH); IR $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3403, 2943, 2877, 1687; ^1H NMR 951
 952 (DMSO- d_6) δ_{H} 7.86 (1H, d, $J = 6.3$ Hz, NH VAL), 7.17 (1H, t, 952
 953 $J = 3.9$ Hz, NH GABA), 5.21 (1H, dd, $J = 3.2, 3.2$ Hz, H12), 953
 954 4.14 (1H, dd, $J = 4.5, 6.3$ Hz, 1H–C2 VAL), 3.41 (1H, ddd, $J =$ 954
 955 4.3, 10.5, 12.2 Hz, H2), 2.96 (2H, m, 2H–C6 6AHA), 2.77 955
 956 (1H, dd, $J = 3.4, 12.5$ Hz, H18), 2.73 (1H, d, $J = 10.5$ Hz, H3), 956
 957 2.20–2.00 (2H, m, 1H–C3 VAL and 1H–C2 6AHA), 0.86 957
 958 (6H, d, $J = 4.5$ Hz, 3H–C4 and 3H–C5 VAL), 1.08, 0.91, 0.88, 958
 959 0.86, 0.86, 0.69, 0.65 (3H each, s, Me groups); ^{13}C NMR 959
 960 (DMSO- d_6) δ_{C} 176.1 (C28), 173.1 (C1 6AHA), 172.4 (C1 960
 961 VAL), 144.2 (C13), 121.2 (C12), 82.2 (C3), 67.1 (C2), 56.9 961

962 (C2 VAL), 54.8 (C5), 47.1 (C9), 46.8 (C1), 46.0 (C19), 45.1
 963 (C17), 41.3 (C14), 40.4 (C18), 39.1 (C10), 38.9 (C4), 38.7
 964 (C6 6AHA), 37.6 (C8), 34.9 (C2 6AHA), 33.6 (C21), 32.9
 965 (Me), 32.7 (C7), 32.4 (C22), 30.4 (C20), 29.8 (C3 VAL), 28.9
 966 (C5 6AHA), 28.8 (Me), 26.9 (C15), 26.2 (C4 6AHA), 25.7
 967 (Me), 25.1 (C3 6AHA), 23.6 (Me), 23.0 (C16), 22.3 (C11),
 968 19.1 (2ME VAL), 18.0 (C6), 17.1 (Me), 16.8 (Me), 16.3 (Me);
 969 ESI-HRMS (*m/z*) [M + Na]⁺ calcd for C₄₁H₆₈N₂O₆Na
 970 707.4975, found 707.4977.

971 *N'*-[N-(2*α*,3*β*-Dihydroxyolean-12-en-28-oyl)-11-aminoun-
 972 decanoyl]-L-valine (24): HPLC retention time 6.52 min;
 973 HPLC purity 100%; white solid; mp 138–140 °C; [α]_D +
 974 24° (c 1, MeOH); IR ν_{max}(KBr)/cm⁻¹ 3411, 2953, 2899, 1699;
 975 ¹H NMR (DMSO-d₆) δ_H 7.84 (1H, d, *J* = 6.0 Hz, NH VAL),
 976 7.15 (1H, t, *J* = 3.9 Hz, NH 11AUA), 5.20 (1H, dd, *J* = 3.2, 3.2
 977 Hz, H12), 4.12 (1H, dd, *J* = 4.5, 6.0 Hz, 1H-C2 VAL), 3.41
 978 (1H, ddd, *J* = 4.3, 10.5, 12.2 Hz, H2), 2.92 (2H, m, 2H-C11
 979 11AUA), 2.77 (1H, dd, *J* = 3.4, 12.5 Hz, H18), 2.73 (1H, d, *J* =
 980 10.5 Hz, H3), 2.13 (1H, dq, *J* = 4.5, 6.0 Hz, 1H-C3 VAL), 2.06
 981 (2H, t, *J* = 4.8 Hz, 2H-C2 11AUA), 0.87 (6H, d, *J* = 4.5 Hz,
 982 3H-C4 and 3H-C5 VAL), 1.06, 0.90, 0.87, 0.86, 0.84, 0.68,
 983 0.63 (3H each, s, Me groups); ¹³C NMR (DMSO-d₆) δ_C 176.0
 984 (C28), 173.2 (C1 11AUA), 172.5 (C1 VAL), 144.3 (C13),
 985 121.2 (C12), 82.2 (C3), 67.1 (C2), 57.0 (C2 VAL), 54.8 (C5),
 986 47.1 (C9), 46.8 (C1), 46.1 (C19), 45.2 (C17), 41.3 (C14), 41.0
 987 (C18), 39.2 (C10), 39.1 (C4), 38.8 (C11 11AUA), 37.6 (C8),
 988 35.0 (C2 11AUA), 33.7 (C21), 32.9 (Me), 32.8 (C7), 32.4
 989 (C22), 30.4 (C20), 30.1 (C10 11AUA), 30.0 (C3 VAL), 29.1
 990 (C6 11AUA), 29.0 (C5 and C7 11AUA), 28.9 (C8 11AUA),
 991 28.8 (C4 11AUA and Me), 26.9 (C15), 26.7 (C9 11AUA), 26.4
 992 (C3 11AUA), 25.7 (Me), 23.6 (Me), 23.0 (C16), 22.3 (C11),
 993 19.2 (2 Me VAL), 18.0 (C6), 17.1 (Me), 16.9 (Me), 16.3
 994 (Me); ESI-HRMS (*m/z*) [M + Na]⁺ calcd for C₄₆H₇₈N₂O₆Na
 995 777.5757, found 777.5764.

996 **General Procedure for the Acylation of Monopeptid-
 997 yl-Resin or Dipeptidyl-Resin Derivatives of OA or MA.**
 998 Having completed the second step of the semisynthesis of the
 999 mono- or dipeptidyl derivatives of OA or MA, we separated an
 1000 aliquot of the derivatives formed to carry out acylation reactions
 1001 on the hydroxyl groups at C-2 or C-2/C-3 of these molecules.
 1002 Then, the corresponding OA- or MA-Aa1-resin derivatives, or
 1003 OA- or MA-Aa1-Aa2-resin derivatives, were treated with a
 1004 solution of the appropriate acid anhydride (3 equiv), DMAP (5
 1005 mg), Et₃N (0.05 mL), in DMF. The mixture was stirred at 40–
 1006 45 °C for 48 h, washed with DMF (2 mL × 3) and DCM (2
 1007 mL × 3), and then drained under reduced pressure. Finally, the
 1008 cleavage of these derivatives from the resin was performed by
 1009 the above-mentioned procedure. Thus, a library of 240
 1010 derivatives of OA or MA (1a–1j to 24a–24j), acylated at C-
 1011 2 or C-2/C-3, and with a mono- or a dipeptidyl group, was
 1012 prepared. The characteristics of all these derivatives are given in
 1013 the Supporting Information.

1014 **Benzylation of Mono- or Dipeptidyl OA Succinyl
 1015 Derivatives.** To determine more accurately the proportion of
 1016 the succinyl derivatives 2h and 8h, we performed a benzylation
 1017 reaction of the free carboxylic acid groups of these compounds.
 1018 Hence, to a solution of each derivative in DMF, BnCl (molar
 1019 relationship BnCl/compound, 2:1) and K₂CO₃ (molar relation-
 1020 ship K₂CO₃/compound, 1:1) were added. The reaction was
 1021 stirred for 4 h at 55 °C. The mixture was diluted with water and
 1022 extracted with DCM, and the organic layer was dried with
 1023 anhydrous Na₂SO₄. The solvent was removed under reduced
 1024 pressure, and the residue was purified by column chromatog-

raphy using DCM/acetone or hexane/AcOEt, to give 1025 compounds 25 (95%) and 26 (98%), respectively. 1026

1027 **Benzyl N-(3*β*-Benzylsuccinylxylolean-12-en-28-oyl)-6-
 1028 aminohexanoate (25):** HPLC retention time 10.41 min; 1029 HPLC purity 95%; colorless oil; [α]_D + 44.2° (c 1, MeOH); IR 1029 ν_{max}(NaCl)/cm⁻¹ 3363, 2953, 2877, 1715; ¹H NMR (Cl₃CD) 1030 δ_H 7.35 (10H, m, benzyl groups), 5.90 (1H, dd, *J* = 3.3, 3.3 Hz, 1031 NH), 5.36 (1H, dd, *J* = 3.4, 3.4 Hz, H12), 5.16–5.10 (4H, m, 1032 benzyl groups), 4.51 (1H, dd, *J* = 4.5, 10.5 Hz, H3), 3.35 (1H, 1033 m, 1H-C6 6AHA), 3.00 (1H, m, 1H-C6 6AHA), 2.75–2.60 1034 (4H, m, succinyl group), 2.50 (1H, dd, *J* = 3.6, 12.7 Hz, H18), 1035 2.36 (2H, t, *J* = 7.0 Hz, 2H-C2 6AHA), 1.14, 0.92, 0.91, 0.91, 1036 0.85, 0.84, 0.76 (3H each, s, Me groups); ¹³C NMR (Cl₃CD) 1037 δ_C 178.2 (C28), 173.5 (C1 6AHA), 172.4 and 172.3 (C1 and 1038 C4 succinyl group), 145.3 (C13), 136.2 and 136.0 (2 C benzyl 1039 groups), 128.7, 128.4, 128.3, 128.2 (10 CH benzyl groups), 1040 122.7 (C12), 81.5 (C3), 66.7 and 66.3 (2 CH₂ benzyl groups), 1041 55.4 (C5), 47.6 (C9), 46.9 (C19), 46.4 (C17), 42.5 (C18), 42.3 1042 (C14), 39.5 (C10), 39.4 (C6 6AHA), 38.3 (C1), 37.9 (C8), 1043 37.0 (C4), 34.3 (C2 6AHA and C21), 33.1 (Me), 32.7 (C7), 1044 32.5 (C22), 30.9 (C20), 29.7 and 29.5 (C2 and C3 succinyl 1045 group), 29.2 (C5 6AHA and C2), 28.2 (Me), 27.5 (C15), 26.7 1046 (C4 6AHA), 25.9 (Me), 24.7 (C3 6AHA), 23.8 (C11 and Me), 1047 23.6 (C16), 18.3 (C6), 17.1 (Me), 16.8 (Me), 15.6 (Me); ESI- 1048 HRMS (*m/z*) [M + 1]⁺ calcd for C₅₄H₇₆NO₇ 850.5622, found 1049 850.5628. 1050

1051 **Benzyl N'-[N-(3*β*-benzylsuccinylxylolean-12-en-28-oyl)-6-
 1052 aminohexanoyl]-glycinate (26):** HPLC retention time 26.92 1052 min; HPLC purity 98%; colorless oil; [α]_D + 37.8° (c 1, 1053 MeOH); IR ν_{max}(NaCl)/cm⁻¹ 3352, 2963, 2887, 1699; ¹H 1054 NMR (Cl₃CD) δ_H 7.35 (10H, m, benzyl groups), 6.06 (1H, 1055 part X of an ABX system, *J* = 3.5, 5.0 Hz, NH GLY), 5.94 (1H, 1056 dd, *J* = 6.0, 6.0 Hz, NH 6AHA), 5.36 (1H, dd, *J* = 3.5, 3.5 Hz, 1057 H12), 5.18–5.09 (4H, m, benzyl groups), 4.51 (1H, dd, *J* = 4.5, 1058 10.5 Hz, H3), 4.06 (2H, part AB of an ABX system, *J* = 3.5, 5.0, 1059 18.4 Hz, 2H-C2 GLY), 3.35 (1H, m, 1H-C6 6AHA), 2.99 1060 (1H, m, 1H-C6 6AHA), 2.70–2.50 (4H, m, succinyl group), 1061 2.51 (1H, dd, *J* = 3.6, 12.7 Hz, H18), 2.24 (2H, t, *J* = 6.5 Hz, 1062 2H-C2 6AHA), 1.15, 0.92, 0.90, 0.90, 0.85, 0.83, 0.76 (3H 1063 each, s, Me groups); ¹³C NMR (Cl₃CD) δ_C 178.3 (C28), 173.1 1064 (C1 6AHA), 172.2 (C1 GLY), 172.0 and 171.1 (C1 and C4 1065 succinyl group), 145.2 (C13), 135.9 and 135.3 (2 C benzyl 1066 groups), 128.9, 128.7, 128.5, and 128.4 (10 CH benzyl groups), 1067 122.7 (C12), 81.4 (C3), 67.3 and 66.6 (2 CH₂ benzyl groups), 1068 55.4 (C5), 47.6 (C9), 46.9 (C19), 46.4 (C17), 42.4 (C18), 42.2 1069 (C14), 41.5 (C2 GLY), 39.5 (C10), 39.3 (C6 6AHA), 38.3 1070 (C1), 37.9 (C8), 37.0 (C4), 36.2 (C2 6AHA), 34.3 (C21), 33.1 1071 (Me), 32.7 (C7), 32.5 (C22), 30.9 (C20), 29.7 and 29.5 (C2 1072 and C3 succinyl group), 29.4 (C2), 29.3 (C5 6AHA), 28.1 1073 (Me), 27.4 (C15), 26.7 (C4 6AHA), 25.8 (Me), 24.7 (C3 1074 6AHA), 23.9 (C11), 23.7 (Me), 23.6 (C16), 18.3 (C6), 17.1 1075 (Me), 16.8 (Me), 15.6 (Me); ESI-HRMS (*m/z*) [M + 1]⁺ calcd 1076 for C₅₆H₇₉N₂O₈ 907.5835, found 907.5844. 1077

1078 **Benzylation of Mono- or Dipeptidyl MA Succinyl
 1079 Derivatives.** Similarly, we also protected the free carboxylic 1080 acid groups of several succinyl derivatives of mono- or 1081 dipeptidyl MA compounds with benzyl chloride. In this case, 1082 not only the 2,3-disuccinyl derivatives (5h and 17h, 1083 respectively) were detected, but also the 2- and 3-succinyl 1084 derivatives. Thus, through the above-mentioned benzylation 1085 procedure, the benzyl succinyl-monopeptidyl MA derivatives 1086 27 (4%), 28 (2%), and 29 (80%); and the benzyl succinyl- 1086

1087 dipeptidyl MA derivatives **30** (5%), **31** (2%), and **32** (85%),
1088 respectively, were obtained.

1089 **Benzyl N-(2α-Benzylsuccinyl)oxy-3β-hydroxyolean-12-en-28-oyl)-6-aminohexanoate (27):** HPLC retention time 25.48
1090 min; HPLC purity 95%; colorless oil; $[\alpha]_D + 3.5^\circ$ (*c* 1,
1092 MeOH); IR $\nu_{\text{max}}(\text{NaCl})/\text{cm}^{-1}$ 3384, 2933, 2891, 1695; ^1H
1093 NMR (Cl_3CD) δ_{H} 7.36–7.33 (10H, m, benzyl groups), 5.90
1094 (1H, dd, *J* = 3.5, 3.5 Hz, NH), 5.35 (1H, dd, *J* = 3.4, 3.4 Hz,
1095 H12), 5.14–5.11 (4H, m, benzyl groups), 5.00 (1H, ddd, *J* =
1096 3.0, 6.5, 10.5 Hz, H2), 3.34 (1H, m, 1H–C6 6AHA), 3.16 (1H,
1097 d, *J* = 6.5 Hz, H3), 2.98 (1H, m, 1H–C6 6AHA), 2.75–2.60
1098 (4H, m, succinyl group), 2.52 (1H, dd, *J* = 3.5, 12.0 Hz, H18),
1099 2.36 (2H, t, *J* = 6.5 Hz, 2H–C2 6AHA), 1.16, 1.06, 1.02, 0.91,
1100 0.88, 0.86, 0.75 (3H each, s, Me groups); ^{13}C NMR (Cl_3CD)
1101 δ_{C} 178.1 (C28), 173.4 (C1 6AHA), 172.7 and 172.6 (C1 and
1102 C4 succinyl group), 145.4 (C13), 136.2, 135.8 (2 C benzyl
1103 groups), 128.8, 128.7, 128.5, and 128.4, (10 CH benzyl
1104 groups), 122.5 (C12), 80.7 (C3), 73.9 (C2), 66.9 and 66.3 (2
1105 CH₂ benzyl groups), 55.2 (C5), 47.6 (C9), 47.0 (C19), 46.4
1106 (C17), 43.7 (C1), 42.4 (C18), 42.3 (C14), 39.8 (C10), 39.6
1107 (C4), 39.4 (C6 6AHA), 38.5 (C8), 34.3 (C2 6AHA and C21),
1108 33.1 (Me), 32.7 (C7), 32.4 (C22), 30.9 (C20), 29.8 and 29.6
1109 (C2 and C3 succinyl group), 29.3 (C5 6AHA), 28.7 (Me), 27.4
1110 (C15), 26.7 (C4 6AHA), 25.9 (Me), 24.7 (C3 6AHA), 23.9
1111 (C11), 23.8 (Me), 23.6 (C16), 18.3 (C6), 17.1 (Me), 16.8
1112 (Me), 16.5 (Me); ESI-HRMS (*m/z*) [M + 1]⁺ calcd for
1113 C₅₄H₇₆NO₈ 866.5571, found 866.5533.

1114 **Benzyl N-(2α-Hydroxy-3β-benzylsuccinyl)oxyolean-12-en-28-oyl)-6-aminohexanoate (28):** HPLC retention time 24.06
1115 min; HPLC purity 94%; colorless oil; $[\alpha]_D + 16.2^\circ$ (*c* 1,
1116 MeOH); IR $\nu_{\text{max}}(\text{NaCl})/\text{cm}^{-1}$ 3377, 2964, 2899, 1700; ^1H
1117 NMR (Cl_3CD) δ_{H} 7.35–7.34 (10H, m, benzyl groups), 5.89
1118 (1H, dd, *J* = 3.5, 3.5 Hz, NH), 5.37 (1H, dd, *J* = 3.4, 3.4 Hz,
1119 H12), 5.17–5.08 (4H, m, benzyl groups), 4.57 (1H, d, *J* = 6.0
1120 Hz, H3), 3.78 (1H, ddd, *J* = 3.0, 6.0, 10.5 Hz, H2), 3.35 (1H,
1121 m, 1H–C6 6AHA), 2.98 (1H, m, 1H–C6 6AHA), 2.75–2.50
1122 (4H, m, succinyl group), 2.50 (1H, dd, *J* = 3.5, 12.0 Hz, H18),
1123 2.36 (2H, t, *J* = 6.5 Hz, 2H–C2 6AHA), 1.16, 0.98, 0.91, 0.91,
1124 0.87, 0.84, 0.76 (3H each, s, Me groups); ^{13}C NMR (Cl_3CD)
1125 δ_{C} 178.2 (C28), 173.4 (C1 6AHA), 173.0 and 172.9 (C1 and
1126 C4 succinyl group), 145.3 (C13), 136.2 and 135.7 (2 C benzyl
1127 groups), 128.8, 128.7, 128.5, and 128.3 (10 CH benzyl groups),
1128 122.6 (C12), 85.5 (C3), 67.2 (C2), 66.9 and 66.3 (2 CH₂
1129 benzyl groups), 55.1 (C5), 47.6 (C9), 47.0 (C19), 46.9 (C1),
1130 46.4 (C17), 42.5 (C18), 42.3 (C14), 39.6 (C10), 39.4 (C6
1131 6AHA and C4), 38.1 (C8), 34.3 (C2 6AHA and C21), 33.1
1132 (Me), 32.7 (C7), 32.4 (C22), 30.8 (C20), 29.7 and 29.6 (C2
1133 and C3 succinyl group), 29.2 (C5 6AHA), 28.6 (Me), 27.4
1134 (C15), 26.7 (C4 6AHA), 25.9 (Me), 24.7 (C3 6AHA), 23.8
1135 (C11), 23.7 (C16 and Me), 18.4 (C6), 17.8 (Me), 17.1 (Me),
1136 16.8 (Me); ESI-HRMS (*m/z*) [M + 1]⁺ calcd for C₅₄H₇₆NO₈
1137 866.5571, found 866.5539.

1138 **Benzyl N-(2α,3β-Dibenzylsuccinyl)oxyolean-12-en-28-oyl)-6-aminohexanoate (29):** HPLC retention time 27.40 min;
1139 HPLC purity 98%; colorless oil; $[\alpha]_D + 12.1^\circ$ (*c* 1, MeOH); IR
1140 $\nu_{\text{max}}(\text{NaCl})/\text{cm}^{-1}$ 3390, 2969, 2895, 1712; ^1H NMR (Cl_3CD)
1141 δ_{H} 7.35–7.30 (15H, m, benzyl groups), 5.88 (1H, dd, *J* = 3.5,
1142 3.5 Hz, NH), 5.35 (1H, dd, *J* = 3.5, 3.5 Hz, H12), 5.15–5.05
1143 (6H, m, benzyl groups), 5.11 (1H, m, H2), 4.78 (1H, d, *J* = 6.5
1144 Hz, H3), 3.36 (1H, m, 1H–C6 6AHA), 2.99 (1H, m, 1H–C6
1145 6AHA), 2.75–2.60 (8H, m, succinyl group), 2.50 (1H, dd, *J* =
1146 3.5, 12.0 Hz, H18), 2.36 (2H, t, *J* = 6.5 Hz, 2H–C2 6AHA),
1147 1.16, 1.04, 0.91, 0.91, 0.88, 0.88, 0.75 (3H each, s, Me groups);

1148 ^{13}C NMR (Cl_3CD) δ_{C} 178.1 (C28), 173.4 (C1 6AHA), 172.2, 1150
1149 172.0, and 172.0 (C1 and C4 succinyl groups), 145.3 1151
1150 (C13), 136.2, 136.0 (3C benzyl groups), 128.7, 128.6, 128.3, 1152
1151 and 128.2 (15 CH benzyl groups), 122.4 (C12), 80.8 (C3), 1153
1152 70.3 (C2), 66.9, 66.5, and 66.2 (3 CH₂ benzyl groups), 54.9 1154
1153 (C5), 47.5 (C9), 46.9 (C19), 46.4 (C17), 44.0 (C1), 42.4 1155
1154 (C18), 42.2 (C14), 39.6 (C10), 39.5 (C4), 39.3 (C6 6AHA), 1156
1155 38.2 (C8), 34.2 (C2 6AHA and C21), 33.1 (Me), 32.7 (C7), 1157
1156 32.3 (C22), 30.8 (C20), 29.4, 29.3, 29.2, and 29.1 (C2 and C3 1158
1157 succinyl groups), 29.3 (C5 6AHA), 28.5 (Me), 27.4 (C15), 1159
1158 26.7 (C4 6AHA), 25.8 (Me), 24.6 (C3 6AHA), 23.8 (C11), 1160
1159 23.7 (C16 and Me), 18.3 (C6), 17.7 (Me), 17.0 (Me), 16.5 1161
1160 (Me); ESI-HRMS (*m/z*) [M + 1]⁺ calcd for C₆₅H₈₆NO₁₁ 1162
1161 1056.6201, found 1056.6215. 1163

1162 **Benzyl N-[N-(2α-Benzylsuccinyl)oxy-3β-hydroxyolean-12-en-28-oyl]-glycinate (30):** HPLC reten- 1164
1163 tion time 27.78 min; HPLC purity 95%; colorless oil; $[\alpha]_D + 1164$
1165 8.0° (*c* 1, MeOH); IR $\nu_{\text{max}}(\text{NaCl})/\text{cm}^{-1}$ 3399, 2952, 2883, 1166
1166 1710; ^1H NMR (Cl_3CD) δ_{H} 7.36–7.35 (10H, m, benzyl 1167
1167 groups), 6.03 (1H, part X of an ABX system, *J* = 3.4, 4.9 Hz, 1168
1168 NH GLY), 5.92 (1H, dd, *J* = 4.0, 4.0 Hz, NH 6AHA), 5.36 1169
1169 (1H, dd, *J* = 3.5, 3.5 Hz, H12), 5.20–5.10 (4H, m, benzyl 1170
1170 groups), 5.00 (1H, ddd, *J* = 3.4, 6.0, 10.5 Hz, H2), 4.07 (2H, 1171
1171 part AB of an ABX system, *J* = 3.4, 4.9, 18.2 Hz, 2H–C2 GLY), 1172
1172 3.35 (1H, m, 1H–C6 6AHA), 3.16 (1H, d, *J* = 6.0 Hz, H3), 1173
1173 3.00 (1H, m, 1H–C6 6AHA), 2.75–2.60 (4H, m, succinyl 1174
1174 group), 2.51 (1H, dd, *J* = 3.4, 12.0 Hz, H18), 2.25 (2H, t, *J* = 1175
1175 6.5 Hz, 2H–C2 6AHA), 1.16, 1.06, 1.03, 0.91, 0.91, 0.87, 0.76 1176
1176 (3H each, s, Me groups); ^{13}C NMR (Cl_3CD) δ_{C} 178.2 (C28), 1177
1177 173.0 (C1 6AHA), 172.7 (C1 GLY), 172.5 and 170.1 (C1 and 1178
1178 C4 succinyl group), 145.3 (C13), 135.8 and 135.3 (2 C benzyl 1179
1179 groups), 128.8, 128.7, 128.5, and 128.4 (10 CH benzyl groups), 1180
1180 122.5 (C12), 80.7 (C3), 73.9 (C2), 67.3 and 66.9 (2 CH₂ 1182
1182 benzyl groups), 55.2 (C5), 47.6 (C9), 47.0 (C19), 46.4 (C17), 1183
1183 43.7 (C1), 42.4 (C18), 42.3 (C14), 41.5 (C2 GLY), 39.8 1184
1184 (C10), 39.6 (C4), 39.3 (C6 6AHA), 38.5 (C8), 36.3 (C2 1185
1185 6AHA), 34.3 (C21), 33.1 (Me), 32.8 (C7), 32.4 (C22), 30.9 1186
1186 (C20), 29.8 and 29.6 (C2 and C3 succinyl group), 29.3 (C5 1187
1187 6AHA), 28.7 (Me), 27.4 (C15), 26.7 (C4 6AHA), 25.9 (Me), 1188
1188 25.1 (C3 6AHA), 23.9 (C11), 23.8 (C16), 23.7 (Me), 18.4 1189
1189 (C6), 17.1 (Me), 16.8 (Me), 16.5 (Me); ESI-HRMS (*m/z*) [M 1190
1190 – 1]⁺ calcd for C₅₆H₇₇N₂O₉, 921.5629, found 923.5615. 1191

1191 **Benzyl N-[N-(2α-Hydroxy-3β-benzylsuccinyl)oxyolean-12-en-28-oyl]-glycinate (31):** HPLC reten- 1192
1192 tion time 27.15 min; HPLC purity 95%; colorless oil; $[\alpha]_D + 1193$
1193 11.4° (*c* 1, MeOH); IR $\nu_{\text{max}}(\text{NaCl})/\text{cm}^{-1}$ 3379, 2953, 2902, 1194
1194 1690; ^1H NMR (Cl_3CD) δ_{H} 7.35–7.30 (10H, m, benzyl 1195
1195 groups), 6.55 (1H, part X of an ABX system, *J* = 3.4, 4.9 Hz, 1196
1196 NH GLY), 5.99 (1H, dd, *J* = 3.5, 3.5 Hz, NH 6AHA), 5.47 1197
1197 (1H, dd, *J* = 3.4, 3.4 Hz, H12), 5.20–5.10 (4H, m, benzyl 1198
1198 groups), 4.57 (1H, d, *J* = 6.0 Hz, H3), 3.95 (2H, part AB of an 1199
1199 ABX system, *J* = 3.4, 4.9, 18.2 Hz, 2H–C2 GLY), 3.78 (1H, 1200
1200 ddd, *J* = 3.0, 6.0, 10.5 Hz, H2), 3.24 (2H, m, 2H–C6 6AHA), 1201
1201 2.75–2.60 (4H, m, succinyl group), 2.58 (1H, dd, *J* = 3.5, 12.0 1202
1202 Hz, H18), 2.35 (2H, t, *J* = 6.5 Hz, 2H–C2 6AHA), 1.17, 0.96, 1203
1203 0.91, 0.91, 0.87, 0.83, 0.69 (3H each, s, Me groups); ^{13}C NMR 1204
1204 (Cl₃CD) δ_{C} 180.2 (C28), 173.5 (C1 6AHA), 173.1 and 173.0 1205
1205 (C1 and C4 succinyl group), 172.4 (C1 GLY), 143.8 (C13), 1206
1206 136.2 and 135.7 (2 C benzyl groups), 128.8, 128.6, 128.5, and 1207
1207 128.2 (10 CH benzyl groups), 123.8 (C12), 85.5 (C3), 67.4 1208
1208 (C2), 67.0 and 66.4 (2 CH₂ benzyl groups), 55.1 (C5), 47.6 1209
1209 (C2), 46.8 (C19), 46.6 (C1), 46.4 (C17), 42.1 (C18), 42.3 1210
1210 (C14), 41.5 (C2 GLY), 39.7 (C6 6AHA), 39.6 (C10), 39.4 1211
1211

1213 (C4), 38.1 (C8), 34.2 (C2 6AHA and C21), 33.1 (Me), 32.5
 1214 (C7), 32.3 (C22), 30.8 (C20), 29.7 and 29.6 (C2 and C3
 1215 succinyl group), 29.2 (C5 6AHA), 28.6 (Me), 27.4 (C15), 26.4
 1216 (C4 6AHA), 25.9 (Me), 24.7 (C3 6AHA), 23.8 (C11), 23.7
 1217 (C16 and Me), 18.4 (C6), 17.8 (Me), 16.8 (Me), 16.7 (Me);
 1218 ESI-HRMS (*m/z*) [M - 1]⁺ calcd for C₅₆H₇₇N₂O₉ 921.5629,
 1219 found 923.5613.
 1220 *Benzyl N'-(N-(2 α ,3 β -Dibenzylsuccinyl)oxyolean-12-en-28-oyl)-6-aminoxylohexanoyl-glycinate* (32): HPLC retention time
 1221 29.75 min; HPLC purity 97%; colorless oil; [α]_D + 12.1° (c 1,
 1222 MeOH); IR ν_{max}(NaCl)/cm⁻¹ 3383, 2939, 2897, 1719; ¹H
 1223 NMR (Cl₃CD) δ_H 7.36–7.25 (1H, m, benzyl groups), 6.05
 1224 (1H, part X of an ABX system, *J* = 3.4, 4.9 Hz, NH GLY), 5.91
 1225 (1H, dd, *J* = 3.0, 3.0 Hz, NH 6AHA), 5.35 (1H, dd, *J* = 3.4, 3.4
 1226 Hz, H12), 5.20–5.05 (6H, m, benzyl groups), 5.10 (1H, m,
 1227 H2), 4.77 (1H, d, *J* = 6.5 Hz, H3), 4.07 (2H, part AB of an
 1228 ABX system, *J* = 3.4, 4.9, 18.2 Hz, 2H–C2 GLY), 3.35 (1H, m,
 1229 1H–C6 6AHA), 2.99 (1H, m, 1H–C6 6AHA), 2.70–2.55 (8H,
 1230 m, succinyl group), 2.52 (1H, dd, *J* = 3.5, 12.0 Hz, H18), 2.24
 1231 (2H, t, *J* = 6.0 Hz, 2H–C2 6AHA), 1.15, 1.04, 0.91, 0.91, 0.88,
 1232 0.88, 0.75 (3H each, s, Me groups); ¹³C NMR (Cl₃CD) δ_C
 1233 178.1 (C28), 173.0 (C1 6AHA), 172.3 (C1 GLY), 172.2 and
 1234 172.0 (C1 and C4 succinyl groups), 145.2 (C13), 136.0, 135.9
 1235 (3C benzyl groups), 128.8, 128.6, 128.4, and 128.2, (15 CH
 1236 benzyl groups), 122.4 (C12), 80.8 (C3), 70.3 (C2), 66.7, 66.6,
 1237 and 66.5 (2 CH₂ benzyl groups), 54.9 (C5), 47.5 (C9), 46.9
 1238 (C19), 46.4 (C17), 44.0 (C1), 42.3 (C18), 42.2 (C14), 41.5
 1239 (C2 GLY), 39.6 (C10), 39.5 (C4), 39.3 (C6 6AHA), 38.2
 1240 (C8), 36.2 (C2 6AHA), 34.3 (C21), 33.1 (Me), 32.8 (C7), 32.3
 1241 (C22), 30.9 (C20), 29.4, 29.3, and 29.1 (C2 and C3 succinyl
 1242 groups), 29.3 (C5 6AHA), 28.5 (Me), 27.4 (C15), 26.7 (C4
 1243 6AHA), 25.8 (Me), 25.1 (C3 6AHA), 23.8 (C11), 23.7 (C16
 1244 and Me), 18.3 (C6), 17.1 (Me), 16.6 (Me), 16.5 (Me); ESI-
 1245 HRMS (*m/z*) [M + 1]⁺ calcd for C₆₇H₈₉N₂O₁₂ 1113.6416,
 1246 found 1113.6410.

1247 **Drugs.** The different compounds used in cell treatment
 1248 were dissolved before use at 10 mg/mL in 50% DMSO. A stock
 1249 solution was frozen and stored at -20 °C. Prior to the
 1250 experiments, this solution was diluted in cell-culture medium.
 1251 **Cell Culture.** Mouse melanoma cells B16–F10 (ATCC no.
 1252 CRL-6475), human colorectal adenocarcinoma cell line HT29
 1253 (ECACC no. 9172201; ATCC no. HTB-38), and human
 1254 hepatocarcinoma cell line Hep G2 (ECACC no. 85011430),
 1255 were cultured in DMEM supplemented with 2 mM glutamine,
 1256 10% heat-inactivated FCS, 10 000 units/mL of penicillin, and
 1257 10 mg/mL of streptomycin. Subconfluent monolayer cells were
 1258 used in all experiments. All cell lines used were provided by the
 1259 cell bank of the University of Granada, Spain.

1260 **Cell-Proliferation Activity Assay.** The effect of treating
 1261 each product upon proliferation in B16–F10 murine melanoma
 1262 cells, HT29 colon carcinoma cells, and Hep G2 hepatocarci-
 1263 nome cells was measured using the MTT assay (Sigma, MO,
 1264 U.S.A.), which is based on the ability of live cells to cleave the
 1265 tetrazolium ring, thus producing formazan, which absorbs at
 1266 570 nm. Cell viability was determined by measuring the
 1267 absorbance of MTT dye staining of living cells. For this assay, 5
 1268 × 10³ B16–F10 cells, 6 × 10³ HT29 cells, and 15 × 10³ Hep
 1269 G2 cells, were grown on a 96-well plate and incubated with the
 1270 different products (0–300 µg/mL). After 72 h, 100 µL of MTT
 1271 solution (0.5 mg/mL) was added to each well. After 2 h of
 1272 incubation, the cells were washed twice with PBS and the
 1273 formazan was resuspended in 200 µL of DMSO. Relative cell
 1274 viability, with respect to untreated control cells, was measured
 1275

by absorbance at 550 nm on an ELISA plate reader (Tecan 1276 Sunrise MR20-301, TECAN, Austria). 1277

■ ASSOCIATED CONTENT 1278

● Supporting Information 1279

ESI-HRMS, HPLC retention time, and HPLC purity data of 1280 compounds 1a–1j to 24a–24j (240-membered library 1281 derivatives). This material is available free of charge via the 1282 Internet at <http://pubs.acs.org>. 1283

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The manuscript was written through contributions of all 1290 authors. All authors have given approval to the final version of 1291 the manuscript. 1292

Notes 1293

The authors declare no competing financial interest. 1294

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■ ABBREVIATIONS 1301

OA, oleanolic acid; MA, maslinic acid; DCM, dichloromethane; 1302 DIEA, *N,N*-diisopropylethylamine; DIPCDI, *N,N'*-diisopropyl- 1303 carbodiimide; PyAOP, 7-azabenzotriazol-1-yloxytris- 1304 (pyrrolidino)phosphonium hexafluorophosphate; HOAt, 1- 1305 hydroxy-7-azabenzotriazole; DMAP, 4-dimethylaminopyridine; 1306 BnCl, benzyl chloride; DMF, dimethylformamide; Et₃N, 1307 triethylamine; DMSO, dimethyl sulfoxide; TFA, trifluoroacetic 1308 acid; MeCN, acetonitrile; CTC-resin, 2-chlorotrityl chloride 1309 polymer resin; DMEM, Dulbecco's modified eagle medium; 1310 FCS, fetal bovine serum; MTT, 3-(4,5-dimethylthiazol-2-yl)- 1311 2,5-diphenyltetrazolium bromide; PBS, phosphate buffered 1312 saline; TLC, thin layer chromatography; Fmoc, fluorenylm- 1313 thyloxycarbonyl chloride; GLY, glycine; ALA, alanine; VAL, 1314 valine; GABA, γ -aminobutyric acid; 6AHA, 6-aminoxylohexanoic 1315 acid; 11AUA, 11-aminoundecanoic acid 1316

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