Synthetic Modification of 9α- and 9β-Hydroxyparthenolide by Heck or Acylation Reactions and Evaluation of Cytotoxic Activities

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Key words
- *Anvillea radiate*
- Asteraceae
- acylation
- cytotoxic activity
- Heck coupling
- 9α-hydroxyparthenolide
- 9β-hydroxyparthenolide

Abstract

Motivated by the widely reported anticancer activity of parthenolides and their derivatives, a series of new substituted parthenolides was efficiently synthesized. Structural modifications were performed at the C-9 and C-13 positions of 9α- and 9β-hydroxyparthenolide, which were isolated from the aerial parts of *Anvillea radiata*. Twenty-one derivatives were synthesized and evaluated for their *in vitro* cytotoxic activity against HS-683, SK-MEL-28, A549, and MCF-7 human cancer cell lines using the MTT colorimetric assay. Among the derivatives, seven exhibited excellent activity compared to 5-fluorouracil and etoposide against the four cell lines tested, with IC_{50} values ranging from 1.1 to 9.4 µM.

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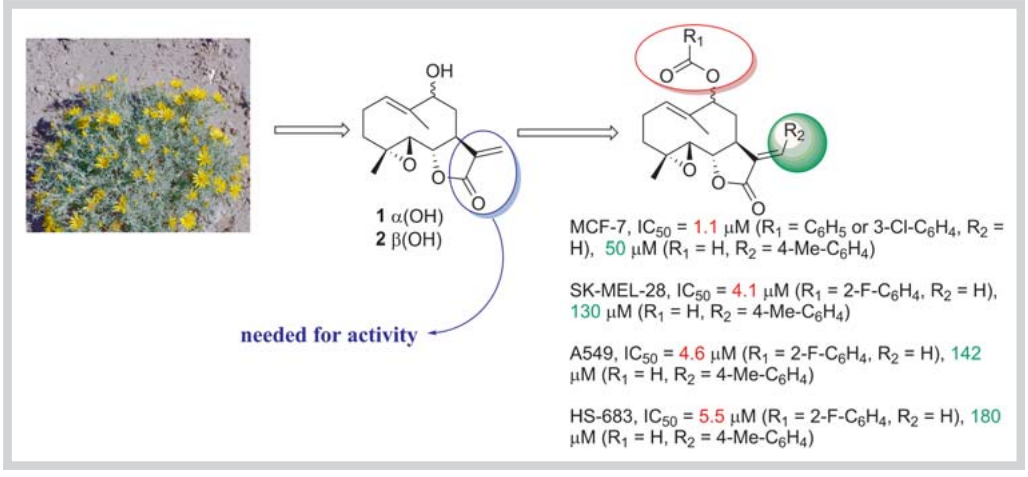

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Bibliography
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Introduction

Cancer is considered one of the most serious health problems and a leading cause of death worldwide [1–3]. Most conventional anticancer drugs have substantial side effects as a result of their lack of selectivity between cancer cells and normal cells [4]. This clearly underlines the urgent need to develop novel chemotherapeutic agents with higher bioactivity and fewer side effects. A large number of biologically active compounds have been obtained from plants. The functionalization of natural products is the most widely used approach for obtaining novel therapeutic agents in medicinal chemistry [5–7]. Parthenolide I (**Fig. 1**) was first isolated from dried, ground *Chrysanthemum parthenium* by Soucek et al. [8]. It was shown to be a sesquiterpene lactone of the germacrane type and a privileged natural product with a wide range of biological activities [9,10]. For example, in traditional herbal medicine, it has been used for the treatment of fever, migraine, and arthritis as well as as an anti-inflammatory agent for centuries [11–13]. Recently, parthenolide and its sesquiterpene lactones were investigated for the treatment of several cancers

[14–18]. The anticancer properties of this drug have been associated to its ability to inhibit the transcription factor NF-κB, which is known to control multiple tumor-related processes such as inflammation, proliferation, angiogenesis, and metastasis [19–21]. However, parthenolide **I** is poorly soluble in water, which limits its potential therapeutic use in humans [22]. DMAPT **II** (**Fig. 1**), the water-soluble dimethylamino Michael adduct of parthenolide **I**, has entered preclinical or clinical trials for the treatment of acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic lymphocytic leukemia (CLL) in the United Kingdom [23,24]. Despite this progress, improvements in parthenolide anticancer potency have not been achieved to date.

In a previous paper [25], we reported the synthesis and anticancer activity evaluation of a series of their 9-hydroxy and 1β-10α-epoxy analogs of types **III, IV**, and **V** (**Fig. 1**). However, the activity of these derivatives was found to be no better than that of their parent compounds 9α- and 9β-hydroxyparthenolide **1** and **2**. The latter were isolated in gram-scale from *Anvillea radiate*, which is a wild plant found mainly in the steppes of North Africa (Morocco and Algeria) and a renewable source of 9α- and 9β-hydroxyparthenolide **1** and **2** [26]. Recently, it was reported that structural modifications at the C9 positions of parthenolide led to derivatives possessing increased antitumor activity [27]. In fact, 9β-hydroxyparthenolide **2** was synthetized by C-9 hydroxylation of parthenolide **I** using enzymatic oxidation. The isolated hydroxylation product **2** was then further processed to generate a panel of 9-substituted parthenolide derivatives, with potent activity and high selectivity against AML cells, using direct acylation of **2** with acyl chloride reagents [27].

We believe that the anticancer properties of 9-hydroxyparthenolide derivatives depend on the structural modifications at the C9 positions and the presence of the α-methylene-γ-lactone moiety. We report herein the synthesis and in *vitro* anticancer evaluation of novel C9- and C13- substituted parthenolides of type **VI, VII**, and **VIII** (**Fig. 1**) with a view to producing promising anticancer agents.

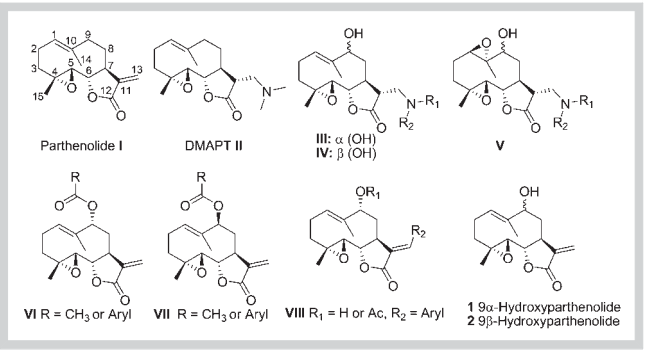


Fig. 1 Some bioactive parthenolide derivatives and target molecules.

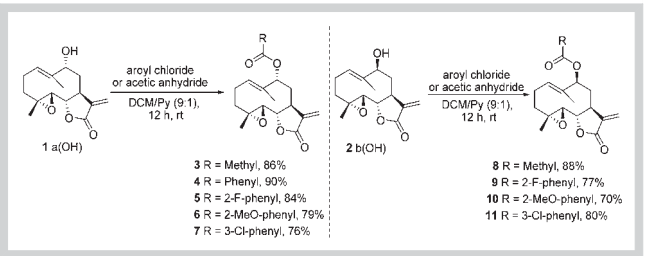


Fig. 2 Acylation of 9α- and 9β-hydroxyparthenolides (**1** and **2**).

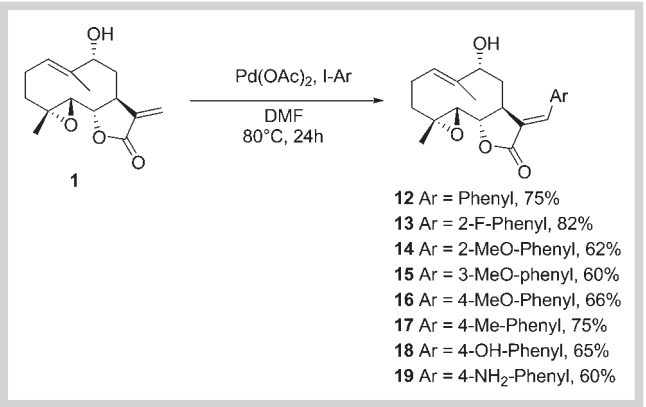


Fig. 3 Heck couplings with 9α-hydroxyparthenolide **1** and aryl iodides.

Results and Discussion

The 9α- and 9β-hydroxyparthenolide **1** and **2** were extracted from the aerial parts of naturally occurring *A. radiata* by soxhlet extraction using ethyl acetate. The concentrated ethyl acetate extract was subjected to column chromatography over silica gel using hexane/ethyl acetate (9/1 up to 6/4) to yield 9α- and 9β-hydroxyparthenolide **1** and **2**. The structure modification of 9α- and 9β-hydroxyparthenolide **1** and **2**, used as the leading compounds, was done at positions C9 and C13.

In our previous report, it was shown that the addition of amines [25] or azide [28] to the α-methylene-γ-lactone of 9-hydroxyparthenolide via Michael addition reactions led to a decrease in antitumor activity. This result demonstrated that the α-methylene-γ-lactone is responsible for the cytotoxic activity.

Based on these observations, we herein report the synthesis and *in vitro* anticancer evaluation of C9-substituted parthenolides (using acylation or arylation reactions), C13-substituted 9α-hydroxyparthenolides (using the Heck reaction to keep the α-methylene-γ-lactone moiety) and C9,C13-disubstituted parthenolides. 9α- and 9β-Hydroxyparthenolide **1** and **2** were reacted with acetic anhydride or aryl chloride in a mixture of dichloromethane/pyridine (9 : 1) at room temperature for 12 h to give the C9-substituted parthenolides **3**–**11** in high yields after purification (**Fig. 2**).

The palladium-catalyzed arylation of the α-methylene-γ-lactone of 9α-hydroxyparthenolide **1** was shown to produce *E*-olefinic coupling products selectively in good yields (60–75%). Novel *E*-olefinic coupling products of 9α-hydroxyparthenolide **1** were prepared under Heck reaction conditions utilizing palladium (II) acetate as the catalyst in DMF and heating the mixture with an appropriate iodo-aromatic compound in the presence of triethylamine for 24 h [29]. After purification by column chromatography, C13-substituted 9α-hydroxyparthenolides **12**–**19** were isolated in good yields (**Fig. 3**). The *E*-olefin for compound **12** was verified using X-ray diffraction (**Fig. 4**). The H13 vinyl proton of compounds **12**–**19** had a chemical shift between 7.46–7.93 ppm. To prepare C9, C13-disubstituted parthenolides **20**–**23**, com-

pounds **12**–**15** were acetylated using 1.3 equivalents of acetic anhydride in a mixture of dichloromethane and pyridine (9 : 1) at room temperature for 12 h. The desired compounds **20**–**23** were obtained in good yields (70–82 %) after purification by column chromatography (**Fig. 5**).

In view of the cytotoxic potential of parthenolide derivatives, the new compounds **4**–**23** were screened for their cytotoxicity against HS-683 (glioma cancer), SK-MEL-28 (melanoma cancer), A549 (Lung cancer), and MCF-7 (breast cancer) cell lines *in vitro* using the MTT assay. The results of cytotoxicity are expressed as the IC_{50} (µM). Etoposide and 5-fluorouracil were used as positive controls. The results are reported in terms of IC_{50} values in **Table 1**. The *c* logP values for these compounds were calculated using ChemBioDraw Ultra v.12 software (**Table 1**). Compounds **4**–**11** showed excellent antiproliferative effects. Among them, compounds **4**–**8, 10**, and **11** displayed potent inhibitory activities, which were more potent than those of the positive control 5-fluorouracil against HS-683, A549, and MCF-7 cells. The 9α-(2-fluorobenzoyloxy)parthenolide **5** was the most potent against HS-683 cells (IC_{50} = 5.5 µM), SK-MEL-28 (IC_{50} = 4.1 µM), and A549 cells (IC_{50} = 4.6 µM), while it exhibited excellent activity against MCF-7 cells (IC_{50} = 2.1 µM). Conversely, 9β-(2-fluorobenzoyloxy)parthenolide **9** was less active than the stereoisomer 9α-(2-fluorobenzoyloxy)parthenolide **5** with an IC_{50} value of 19.4 µM for HS-683, 11.5 µM for SK-MEL-28, and 11.2 µM for A549 cells. Compound **9** exhibited similar activity to **5** against MCF-7 (IC_{50} = 2.0 µM).

9α-Hydroxyparthenolide **1** was of particular interest to us, because it is a valuable intermediate, not accessible via currently available synthetic methods. Compared with 9α-substituted-oxyparthenolide derivatives **4**–**7**, 9β-substituted-oxyparthenolide derivatives **8**–**11** displayed lower antiproliferative activities.

As shown in **Table 1**, C13-substituted-9α-hydroxyparthenolide derivatives **12**–**19** exhibited a large decrease or complete loss of cytotoxic activity compared with 9α-substituted-oxyparthenolides **4**–**7** or 9α-hydroxyparthenolide **1** [25].

Compounds **12**–**15** were acetylated to obtain C13-substituted-9α-acetoxyparthenolide derivatives **20**–**23**. As expected, the antiproliferative effects of compounds **20**–**23** were not improved in comparison with compounds **12**–**19** (**Table 1**).

This result confirms that the α-methylene-γ-lactone moiety unsubstituted at C13-position is very important for cytotoxic activity. It is also critical for mediating parthenolide pharmacological effects, serving as an electrophilic center in Michael-type addition reactions with sulphydryl groups in the various cellular components (e.g., NF-κB, IκK, glutathione) targeted by the molecule [27, 30].

In conclusion, a series of C9-, C13-substituted-9α-hydroxyparthenolide and C9, C13-disubstituted parthenolide derivatives were efficiently synthesized and tested for their cytotoxic activities against four human cancer cell lines. *In vitro* bioassays demonstrated that C9-substituted parthenolide derivatives **4**–**11** displayed good to excellent cytotoxic activities against HS-683 (IC_{50} = 5.5 µM as compound **5**), SK-MEL-28 (IC_{50} = 4.1 µM as compound **5**), A549 (IC_{50} = 4.6 µM as compound **5**), and MCF-7 cell lines (IC_{50} = 1.1 µM as compounds **11** and **4**). We have shown that the modifications of 9α-hydroxyparthenolide at the C13 position led to a decrease in its cytotoxicity, and that the α-methylene-γ-lactone moiety free at the C13 position is necessary for activity. Further structural optimization of substituted-parthenolide derivatives is well under way with the aim of improving their level of antitumor potency.

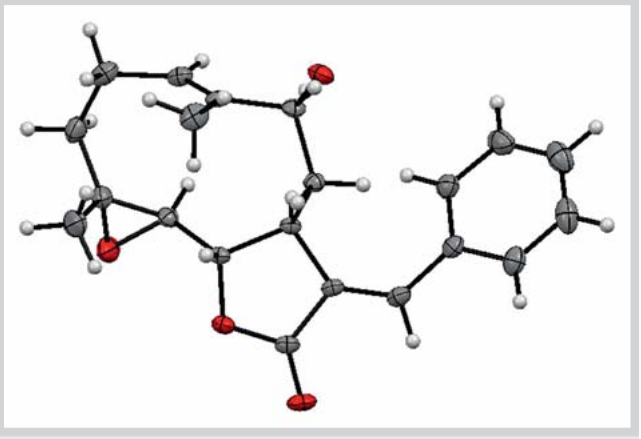


Fig. 4 ORTEP of compound **12** (probability 50 %). (Color figure available online only.)

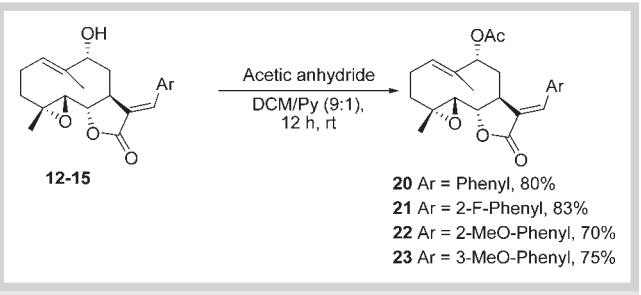


Fig. 5 Acetylation of 9α-hydroxy-13-substituted parthenolides.

Material and Methods

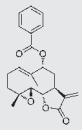
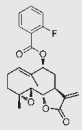
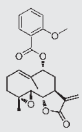
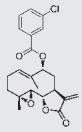
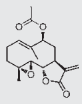
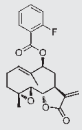
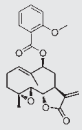
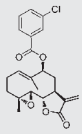
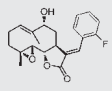
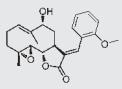
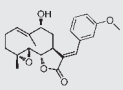
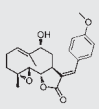
General experimental procedures

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 MHz instrument using $CDCl_3$. The chemical shifts are reported in parts per million (δ scale) and all coupling constant (*J*) values are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet doublet). Melting points are uncorrected. HRMS were recorded on a Bruker maXis mass spectrometer. Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F_{254}). Spots were visualized on TLC plates under UV or by heating silica gel plates sprayed with 5 % phosphomolibdic acid in EtOH. Column chromatographies were performed using silica gel 60 (0.063–0.200 mm, Merck).

Plant material

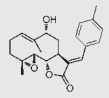
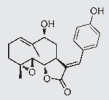
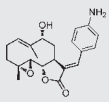
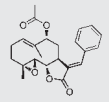
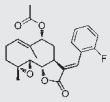
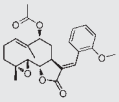
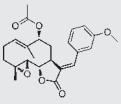
The aerial parts of *A. radiata* (Coss. & Durieu) were collected by the team of Professor El Oualidi Jalal during the flowering period in May 2011 (second week) from Errachidia Road P21, Morocco. GPS coordinates were: Latitude (32.204 086 355 917 944) and Longitude (−4.383 201 599 121 094). A voucher specimen has been deposited in the Herbarium of the Scientific Institute, Rabat, Morocco (No. RAB9913). The harvested parts were screened and freed of contaminating portions and then shade dried at room temperature. After drying, the plant material was stocked in the dark in the lab and was ground to a fine powder using a basic

Table 1 Cytotoxic activity.

Compound	N°	Human cancer cell lines IC_{50} (μM)[1]				c Log P
		HS-683 glioma	SK-MEL-28 melanoma	A549 lung cancer	MCF-7 breast cancer	
	**4**	**5.9** (0.6–11.2)	**5.2** (1.6–8.8)	**5.2** (2.2–8.2)	**1.1** (0.7–1.5)	3.11
	**5**	**5.5** (2.7–8.3)	**4.1** (2.9–5.3)	**4.6** (3.4–5.8)	**2.1** (0.1–4.1)	3.27
	**6**	**7.9** (5.5–9.3)	**6.3** (2.5–10.1)	**5.8** (2.8–8.8)	**1.2** (0.7–1.7)	2.98
	**7**	**6.2** (3.2–9.2)	**7.8** (4.7–10.9)	**8.3** (3.3–13.3)	**1.4** (0.6–2.2)	3.67
	**8**	**7.4** (5.3–9.5)	**5.7** (3.8–7.6)	**5.0** (2.6–7.4)	**2.7** (0.2–5.2)	1.21
	**9**	**19.4** (4.4–34.4)	**11.5** (8.3–14.7)	**11.2** (4.5–16.9)	**2.0** (1.2–2.8)	3.27
	**10**	**8.2** (5.3–10.1)	**5.7** (3–8.4)	**8.9** (6.9–10.9)	**2.3** (1.4–3.2)	2.98
	**11**	**9.4** (5.8–13.0)	**6.4** (4.1–8.7)	**7.3** (3.3–11.3)	**1.1** (0.3–1.9)	3.67
	**12**	**230** (196–264)	**213** (153–273)	**175** (149–201)	**176** (142–210)	2.54
	**13**	*	*	**200** (152–248)	*	2.70
	**14**	**	*	**200** (128–272)	**174** (74–274)	2.41
	**15**	**	*	**200** (152–248)	**200** (100–300)	2.41
	**16**	**	*	**200** (100–300)	*	2.41

continued

Table 1 *Continued*

Compound	N°	Human cancer cell lines IC_{50} (μM)[1]				*c* Log P
		HS-683 glioma	SK-MEL-28 melanoma	A549 lung cancer	MCF-7 breast cancer	
	**17**	**180** (130–230)	**130** (112–138)	**142** (118–166)	**50** (26–74)	3.02
	**18**	**	**200** (140–260)	**190** (158–222)	**134** (72–196)	2.15
	**19**	*	*	*	**103** (45–161)	1.73
	**20**	*	*	*	**163** (47–279)	2.77
	**21**	*	**160** (152–168)	**229** (187–271)	**157** (79–235)	2.92
	**22**	*	*	**205** (143–267)	**132** (84–180)	2.64
	**23**	*	*	**	**169** (85–253)	2.64
Etoposide		**4.0** (3.4–4.6)	**6.5** (5.5–7.5)	**3.0** (2.0–4.0)	**25.0** (23.4–26.6)	
5-Fluorouracile		**16.7** (1.4–32.0)	**13.4** (10.2–16.6)	**3.5** (2.9–4.1)	**19.5** (15.5–23.5)	

[1] IC_{50} values (μM): drug concentration responsible for the inhibition of 50% of the growth of the specified cell line after 72 h. Values are the geometric mean 50% inhibitory concentration; 95% confidence limits are given in brackets. Final DMSO concentration is less than 1% (see experimental part). *Growth reduced by 20–30% at 200 μM. **No growth inhibition detected at 200 μM.

grinder just before extraction. The air-dried aerial parts of *A. radiata* (500 g) were extracted using a soxhlet apparatus with ethyl acetate. After concentration under reduced pressure, the residue (30 g, 6%) was chromatographed over a silica gel column with a gradient of hexane/EtOAc to give 5 g of 9α-hydroxyparthenolide **1** (1%) and 3 g of 9β-hydroxyparthenolide **2** (0.6%).

General procedure to prepare compounds 3–11

Aroyl chloride or acetic anhydride (0.65 mmol) at 0 °C was added to a solution of 9α- or 9β-hydroxyparthenolide (134 mg, 0.5 mmol) in a dry mixture of CH_2Cl_2 and pyridine (9 : 1) (20 mL). The solution was stirred at room temperature for 12 h and poured into saturated aqueous NH_4Cl (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by column chromatography (PE-EtOAc, 8 : 2) provided compounds **3**–**11** as a white oil.

9α-Acetoxyparthenolide (3)

$[\alpha]_D^{20}$ – 6.0 (*c* 1.0, CH_2Cl_2); yield = 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26–1.30 (m, 1H), 1.32 (s, 3H), 1.79 (s, 3H), 1.94–2.07 (m, 1H), 2.16 (s, 3H), 2.17–2.31 (m, 2H), 2.42–2.52 (m, 2H), 2.76 (d, *J* = 8.5 Hz, 1H), 3.24 (t, *J* = 8.0 Hz, 1H), 3.91 (t, *J* = 8.5 Hz, 1H), 5.22 (d, *J* = 5.7 Hz, 1H), 5.45 (d, *J* = 10.8 Hz, 1H), 5.59 (d, *J* = 3.0 Hz, 1H), 6.35 (d, *J* = 3.0 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.4 (CH_3, C-14), 17.2 (CH_3, C-15), 21.1 (CH_3, CH_3CO_2R), 23.5 (CH_2, C-2), 35.6 (CH_2, C-3), 36.1 (CH_2, C-8), 38.7 (CH, C-7), 61.3 (C_q, C-4), 66.5 (CH, C-5), 73.2 (CH, C-9), 82.2 (CH, C-6), 121.4 (CH_2, C-13), 122.6 (CH, C-1), 133.5 (C_q, C-10), 139.2 (C_q, C-11), 168.9 (CO, C-12) 169.5 (CO) ppm. IR (ATR diamond): *v* = 2932, 1760, 1729, 1376, 1123, 1010, 985 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{23}O_5$ [M + H]+ 307.1540, found 307.1540.

9α-Benzoyloxyparthenolide (4)

$[\alpha]_D^{20}$ – 5.4 (*c* 1.0, CH_2Cl_2); yield = 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.33 (m, 1H), 1.35 (s, 3H), 1.87 (s, 3H), 2.06–2.32 (m, 3H), 2.39–2.69 (m, 2H), 2.81 (d, *J* = 8.5Hz, 1H), 3.34–3.49 (m, 1H), 3.97 (t, *J* = 8.5 Hz, 1H), 5.45 (d, *J* = 5.7 Hz, 1H), 5.51–5.60 (m, 1H), 5.64 (d, *J* = 3.5 Hz, 1H), 6.34 (d, *J* = 3.5 Hz, 1H), 7.44–7.55 (m, 2H), 7.59–7.67 (m, 1H), 8.03–8.08 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.5 (CH_3, C-14), 17.3 (CH_3, C-15), 23.5 (CH_2, C-2), 35.8 (CH_2, C-3), 36.1 (CH_2, C-8), 38.9 (CH, C-7), 61.3 (C_q, C-4), 66.7 (CH, C-5), 73.7 (CH, C-9), 82.2 (CH, C-6), 121.6 (CH_2, C-13), 122.7 (CH, C-1), 128.5 (CH_{ar}), 128.7 (CH_{ar}), 129.5 (CH_{ar}), 129.7 (C_{ar}), 130.2 (CH_{ar}), 133.6 (C_q, C-10), 133.7 (CH_{ar}), 139.2 (C_q, C11), 165.0 (CO),

169.0 (CO, C-12) (ppm. IR (ATR diamond): ν = 2933, 1765, 1722, 1314, 1269, 1177, 1139, 987, 727, 711 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{25}O_5$ [M + H]+ 369.1697, found 369.1696.

9α-(2-Fluorobenzoyloxy)parthenolide (5)

$[\alpha]_D^{20}$ − 2.1 (*c* 1.0, CH_2Cl_2); yield = 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26–1.33 (m, 1H), 1.34 (s, 3H), 1.86 (s, 3H), 2.09–2.30 (m, 3H), 2.51 (qd, *J* = 13.1, 5.6 Hz, 1H), 2.61 (dd, *J* = 15.6, 6.0 Hz, 1H), 2.81 (d, *J* = 8.5 Hz, 1H), 3.38 (t, *J* = 7.8 Hz, 1H), 3.96 (t, *J* = 8.5 Hz, 1H), 5.45 (d, *J* = 5.7 Hz, 1H), 5.54 (d, *J* = 9.9 Hz, 1H), 5.62 (d, *J* = 3.2 Hz, 1H), 6.34 (d, *J* = 3.2 Hz, 1H), 7.32 (td, *J* = 8.3, 1.0 Hz, 1H), 7.48 (dd, *J* = 13.7, 7.8 Hz, 1H), 7.72 (d, *J* = 9.1 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.6 (CH_3, C-14), 17.3 (CH_3, C-15), 23.5 (CH_2, C-2), 35.8 (CH_2, C-3), 36.1 (CH_2, C-8), 38.8 (CH, C-7), 61.3 (C_q, C-4), 66.6 (CH, C-5), 74.2 (CH, C-9), 82.2 (CH, C-6), 116.4 (d, *J* = 23.0 Hz, CH_{ar}), 120.6 (d, *J* = 21.3 Hz, CH_{ar}), 121.6 (CH_2, C-13), 122.8 (CH, C-1), 125.2 (d, *J* = 3.1 Hz, CH_{ar}), 130.4 (d, *J* = 7.8 Hz, CH_{ar}), 131.9 (d, *J* = 7.4 Hz, C_{ar}), 133.4 (C_q, C-10), 139.1 (C_q, C-11), 162.6 (d, *J* = 247.9 Hz, C_{ar}), 163.9 (d, *J* = 3.0 Hz, CO), 168.9 (CO, C-12) ppm. IR (ATR diamond): ν = 2934, 1766, 1720, 1269, 1234, 1138, 1094, 1013, 910, 796, 755, 727 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{24}FO_5$ [M + H]+ 387.1602, found 387.1602.

9α-(2-Methoxybenzoyloxy)parthenolide (6)

$[\alpha]_D^{20}$ − 8.0 (*c* 1.0, CH_2Cl_2); yield = 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21–1.32 (m, 1H), 1.34 (s, 3H), 1.85 (s, 3H), 2.01–2.30 (m, 3H), 2.40–2.67 (m, 2H), 2.79 (d, *J* = 9.0 Hz, 1H), 3.43–3.54 (m, 1H), 3.88 (s, 3H), 3.96 (t, *J* = 9.0 Hz, 1H), 5.45 (d, *J* = 6.0 Hz, 1H), 5.57–5.60 (m, 1H), 5.64 (d, *J* = 3.5 Hz, 1H), 6.34 (d, *J* = 3.5 Hz, 1H), 7.00–7.08 (m, 2H), 7.48–7.59 (m, 1H), 7.86 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.4 (CH_3, C-14), 17.3 (CH_3, C-15), 23.6 (CH_2, C-2), 35.7 (CH_2, C-3), 36.3 (CH_2, C-8), 39.0 (CH, C-7), 55.8 (OCH_3), 61.3 (C_q, C-4), 66.6 (CH, C-5), 73.8 (CH, C-9), 82.3 (CH, C-6), 112.1 (CH_{ar}), 119.4 (C_{ar}), 120.4 (CH_{ar}), 121.5 (CH_2, C-13), 122.9 (CH, C-1), 132.0 (CH_{ar}), 133.3 (C_q, C-10), 134.1 (CH_{ar}), 139.3 (C_q, C-11), 159.3 (C_{ar}), 165.1 (CO), 169.1 (CO, C-12) ppm. IR (ATR diamond): ν = 2934, 1765, 1721, 1465, 1489, 1276, 1181, 1165, 1131, 1020, 910, 868, 757, 727 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{27}O_6$ [M + H]+ 399.1802, found 399.1800.

9α-(3-Chloroybenzoyloxy)parthenolide (7)

$[\alpha]_D^{20}$ + 1.4 (*c* 1.0, CH_2Cl_2); yield = 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–1.32 (m, 1H), 1.34 (s, 3H), 1.86 (s, 3H), 2.09–2.31 (m, 3H), 2.51 (qd, *J* = 13.1, 5.5 Hz, 1H), 2.62 (dd, *J* = 15.6, 6.0 Hz, 1H), 2.81 (d, *J* = 8.5 Hz, 1H), 3.36 (t, *J* = 7.8 Hz, 1H), 3.96 (t, *J* = 8.5 Hz, 1H), 5.44 (d, *J* = 5.7 Hz, 1H), 5.54 (d, *J* = 10.0 Hz, 1H), 5.63 (d, *J* = 3.2 Hz, 1H), 6.35 (d, *J* = 3.2 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 8.00 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.6 (CH_3, C-14), 17.3 (CH_3, C-15), 23.5 (CH_2, C-2), 35.8 (CH_2, C-3), 36.1 (CH_2, C-8), 38.8 (CH, C-7), 61.2 (C_q, C-4), 66.6 (CH, C-5), 74.2 (CH, C-9), 82.2 (CH, C-6), 121.6 (CH_2, C-13), 122.9 (CH, C-1), 127.6 (CH_{ar}), 129.6 (CH_{ar}), 130.1 (CH_{ar}), 131.5 (C_{ar}), 133.4 (CH_{ar}), 133.6 (C_q, C-10), 134.9 (C_{ar}), 139.1 (C_q, C-11), 163.9 (CO), 168.8 (CO, C-12) ppm. IR (ATR diamond): ν = 2933, 1766, 1719, 1278, 1253, 1072, 1012, 943, 727 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{24}ClO_5$ [M + H]+ 403.1307, found 403.1306.

9β-Acetoxyparthenolide (8)

$[\alpha]_D^{20}$ − 24.6 (*c* 1.0, CH_2Cl_2); yield = 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.31 (m, 1H), 1.34 (s, 3H), 1.76 (s, 3H), 1.97–2.09 (m, 1H), 2.11 (s, 3H), 2.17–2.30 (m, 3H), 2.50 (qd, *J* = 13.0, 5.1 Hz, 1H), 2.73 (d, *J* = 8.6 Hz, 1H), 2.94 (t, *J* = 8.3 Hz, 1H), 3.87 (t, *J* = 8.6 Hz, 1H), 5.22 (d, *J* = 10.8 Hz, 1H), 5.53 (d, *J* = 10.4 Hz, 1H), 5.71 (d, *J* = 3.2 Hz, 1H), 6.38 (d, *J* = 3.2 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.7 (CH_3, C-14), 17.3 (CH_3, C-15), 21.2 (CH_3, CH_3CO_2R), 23.7 (CH_2, C-2), 36.0 (CH_2, C-3), 36.1 (CH_2, C-8), 44.1 (CH, C-7), 61.3 (C_q, C-4), 66.0 (CH, C-5), 80.7 (CH, C-9), 81.6 (CH, C-6), 121.9 (CH_2, C-13), 127.8 (CH, C-1), 133.0 (C_q, C-10), 138.0 (C_q, C-11), 168.6 (CO, C-12), 170.0 (CO) ppm. IR (ATR diamond): ν = 2931, 1760, 1724, 1374, 1238, 1126, 1016, 986, 946, 890, 868, 812 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{23}O_5$ [M + H]+ 307.1540, found 307.1538.

9β-(2-Fluorobenzoyloxy)parthenolide (9)

$[\alpha]_D^{20}$ − 5.2 (*c* 1.0, CH_2Cl_2); yield = 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27–1.35 (m, 1H), 1.38 (s, 1H), 1.86 (s, 1H), 2.14–2.24 (m, 2H), 2.30–2.39 (m, 2H), 2.53 (qd, *J* = 13.1, 5.1 Hz, 1H), 2.78 (d, *J* = 8.7 Hz, 1H), 3.03 (t, *J* = 8.3 Hz, 1H), 3.93 (t, *J* = 8.7 Hz, 1H), 5.48 (d, *J* = 10.8 Hz, 1H), 5.63 (d, *J* = 10.3 Hz, 1H), 5.75 (d, *J* = 3.0 Hz, 1H), 6.40 (d, *J* = 3.0 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.47 (dd, *J* = 13.6, 7.8 Hz, 1H), 7.73 (d, *J* = 9.1 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.9 (CH_3, C-14), 17.4 (CH_3, C-15), 23.8 (CH_2, C-2), 36.0 (CH_2, C-3), 36.1 (CH_2, C-8), 44.0 (CH, C-7), 61.3 3 (C_q, C-4), 66.0 (CH, C-5), 81.6 (CH, C-9), 81.7 (CH, C-6), 116.5 (d, *J* = 23.0 Hz, CH_{ar}), 120.4 (d, *J* = 21.3 Hz, CH_{ar}), 122.1 (CH_2, C-13), 125.4 (d, *J* = 3.1 Hz, CH_{ar}), 128.2 (CH, C-1), 130.2 (d, *J* = 7.8 Hz, CH_{ar}), 132.2 (d, *J* = 7.4 Hz, C_{ar}), 132.8 (C_q, C-10), 137.9 (C_q, C-11), 162.6 (d, *J* = 247.4 Hz, C_{ar}), 164.3 (d, *J* = 3.0 Hz, CO), 168.6 (CO, C-12) ppm. IR (ATR diamond): ν = 2929, 1769, 1720, 1327, 1313, 1277, 1268, 1251, 1239, 1094, 1021, 978, 965, 944, 889, 793, 748 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{24}FO_5$ [M + H]+ 387.1602, found 387.1602.

9β-(2-Methoxybenzoyloxy)parthenolide (10)

$[\alpha]_D^{20}$ − 12.1 (*c* 1.0, CH_2Cl_2); yield = 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.33 (m, 1H), 1.35 (s, 3H), 1.85 (s, 3H), 2.03–2.22 (m, 2H), 2.27–2.37 (m, 2H), 2.51 (qd, *J* = 13.0, 5.1 Hz, 1H), 2.77 (d, *J* = 8.8 Hz, 1H), 3.01 (t, *J* = 8.3 Hz, 1H), 3.88–3.91 (m, 4H), 5.45 (d, *J* = 10.6 Hz, 1H), 5.58 (d, *J* = 10.0 Hz, 1H), 5.75 (d, *J* = 3.0 Hz, 1H), 6.36 (d, *J* = 3.0 Hz, 1H), 7.00 (dd, *J* = 7.9, 4.1 Hz, 2H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.9 (CH_3, C-14), 17.3 (CH_3, C-15), 23.8 (CH_2, C-2), 36.0 (CH_2, C-3), 36.2 (CH_2, C-8), 44.1 (CH, C-7), 55.9 (OCH_3), 61.3 (C_q, C-4), 66.0 (CH, C-5), 81.1 (CH, C-9), 81.7 (CH, C-6), 112.1 (CH_{ar}), 119.7 (C_{ar}), 120.2 (CH_{ar}), 122.1 (CH_2, C-13), 127.6 (CH, C-1), 131.7 (CH_{ar}), 133.2 (C_q, C-10), 133.9 (CH_{ar}), 138.0 (C_q, C-11), 159.4 (C_{ar}), 165.0 (CO), 168.8 (CO, C-12) ppm. IR (ATR diamond): ν = 2933, 1758, 1716, 1437, 1405, 1394, 1336, 1260, 1229, 1201, 1182, 1066, 1021, 898, 787, 765 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{27}O_6$ [M + H]+ 399.1802, found 399.1802.

9β-(3-Chlorobenzoyloxy)parthenolide (11)

$[\alpha]_D^{20}$ − 8.9 (*c* 1.0, CH_2Cl_2); yield = 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.34 (m, 1H), 1.36 (s, 3H), 1.85 (s, 3H), 2.24–2.15 (m, 2H), 2.28–2.37 (m, 2H), 2.52 (qd, *J* = 13.1, 5.1 Hz, 1H), 2.77 (d, *J* = 8.7 Hz, 1H), 3.03 (t, *J* = 8.3 Hz, 1H), 3.92 (t, *J* = 8.7 Hz, 1H), 5.47 (d, *J* = 10.6 Hz, 1H), 5.62 (d, *J* = 9.9 Hz, 1H), 5.73 (d, *J* = 3.0 Hz, 1H), 6.37 (d, *J* = 3.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.9 (CH_3, C-14), 17.4 (CH_3, C-15), 23.8 (CH_2, C-2), 36.0 (CH_2, C-3), 36.1 (CH_2, C-8), 44.0 (CH, C-7), 61.3 (C_q, C-4), 66.0 (CH, C-5), 81.6 (CH, C-9), 81.7 (CH, C-6), 122.0 (CH_2, C-13), 127.7 (CH, C-1), 128.3 (CH_{ar}), 129.6 (CH_{ar}), 129.9 (CH_{ar}), 131.8 (C_{ar}), 132.7 (C_q, C-10), 133.3 (CH_{ar}), 134.6 (C_{ar}), 137.9 (C_q, C-11), 164.2 (CO),

168.6 (CO, C-12) ppm. IR (ATR diamond): ν = 2933, 1767, 1716, 1315, 1280, 1253, 1020, 908, 795, 728 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{24}ClO_5$ [M + H]+ 403.1307, found 403.1307.

General procedure to prepare compounds 12–19

A mixture of 9α-hydroxyparthenolide (108 mg, 0.4 mmol), triethylamine (1.2 mmol, 3 equivalents), and iodoaryl (0.45 mmol) in DMF (2 mL) was treated with palladium (II) acetate (5 mg, 0.02 mmol) and then heated at 80 °C. After 24 h, the reaction mixture was allowed to cool to room temperature, water (10 mL) was added, and the resulting mixture was extracted with Et_2O (10 mL × 5). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (PE-EtOAc, 8 : 2 up to 0 : 10) afforded compounds **12**–**19**.

9α-Hydroxy-13-phenylparthenolide (12)

$[\alpha]_D^{20}$ + 173.5 (*c* 1.0, CH_2Cl_2); yield = 75%; m.p. 250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29–1.39 (m, 1H), 1.35 (s, 3H), 1.62–1.65 (m, 1H), 1.67 (s, 3H), 1.82 (s, 1H), 2.21 (ddd, *J* = 7.0, 4.7, 1.8 Hz, 1H), 2.31 (d, *J* = 13.5 Hz, 1H), 2.47–2.62 (m, 2H), 2.87 (d, *J* = 7.6 Hz, 1H), 3.92–3.96 (m, 2H), 4.20 (d, *J* = 4.8 Hz, 1H), 5.71 (ddd, *J* = 12.3, 2.7, 1.2 Hz, 1H), 7.38–7.46 (m, 3H), 7.70 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.73 (d, *J* = 1.5 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 (CH_3, C-14), 17.6 (CH_3, C-15), 23.9 (CH_2, C-2), 35.0 (CH_2, C-3), 35.9 (CH_2, C-8), 37.8 (CH, C-7), 61.5 (C_q, C-4), 66.4 (CH, C-5), 72.0 (CH, C-9), 81.9 (CH, C-6), 122.5 (CH, C-1), 128.4 (2 × CH_{ar}), 128.6 (C_{ar}), 129.7 (CH_{ar}), 130.9 (2 × CH_{ar}), 133.2 (C_q, C-11), 137.5 (C_q, C-10), 138.5 (CH, C-13), 171.2 (CO, C-12) ppm. IR (ATR diamond): ν = 3363, 2933, 1720, 1648, 1622, 1592, 1199, 1170, 1070, 872, 762, 688 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{25}O_4$ [M + H]+ 341.1744, found 341.1747. Crystallographic data for the structure **12** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1 402 812 (**12**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax:+44 (1223)336 033; E-mail: deposit@ccdc.cam.ac.uk].

9α-Hydroxy-13-(2-fluorophenyl)parthenolide (13)

$[\alpha]_D^{20}$ + 251.1 (*c* 1.0, CH_2Cl_2); yield = 82%; m.p. 220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28–1.38 (m, 1H), 1.35 (s, 3H), 1.60 (s, 1H), 1.66 (s, 3H), 1.69–1.71 (m, 1H), 2.19–2.23 (m, 1H), 2.30 (d, *J* = 13.5 Hz, 1H), 2.45–2.58 (m, 2H), 2.87 (d, *J* = 7.9 Hz, 1H), 3.90–3.97 (m, 2H), 4.16 (dd, *J* = 5.9, 2.3 Hz, 1H), 5.70 (dd, *J* = 12.3, 3.8 Hz, 1H), 7.14 (t, *J* = 9.0 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.40 (td, *J* = 7.4, 1.3 Hz, 1H), 7.82–7.86 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 (CH_3, C-14), 17.5 (CH_3, C-15), 23.9 (CH_2, C-2), 35.1 (CH_2, C-3), 35.9 (CH_2, C-8), 37.9 (CH, C-7), 61.5 (C_q, C-4), 66.3 (CH, C-5), 71.8 (CH, C-9), 82.0 (CH, C-6), 115.6 (d, *J* = 21.6 Hz, CH_{ar}), 121.4 (d, *J* = 13.2 Hz, C_{ar}), 122.5 (CH, C-1), 123.8 (d, *J* = 3.7 Hz, CH_{ar}), 130.6 (d, *J* = 4.9 Hz, CH_{ar}), 131.0 (C_q, C-11), 131.5 (d, *J* = 3.6 Hz, CH_{ar}), 131.6 (d, *J* = 2.9 Hz, CH, C-13), 137.3 (C_q, C-10), 161.0 (d, *J* = 252.3 Hz, C_{ar}), 170.6 (CO, C-12) ppm. IR (ATR diamond): ν = 3487, 2953, 1719, 1651, 1523, 1369, 1350, 1248, 1224, 1109, 1088, 1062, 910, 815, 754, 740 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{24}FO_4$ [M + H]+ 359.1649, found 359.1653.

9α-Hydroxy-13-(2-methoxyphenyl)parthenolide (14)

$[\alpha]_D^{20}$ + 194.2 (*c* 1.0, CH_2Cl_2); yield = 62%; m.p. 168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27–1.37 (m, 1H), 1.33 (s, 3H), 1.59–1.65 (m, 1H), 1.64 (s, 3H), 1.81 (s, 1H), 2.19 (ddd, *J* = 7.5, 4.7, 1.8 Hz, 1H), 2.29 (d, *J* = 13.5 Hz, 1H), 2.44–2.56 (m, 2H), 2.86 (d, *J* = 7.5 Hz, 1H), 3.86–3.93 (m, 2H), 3.89 (s, 3H), 4.11 (d, *J* = 4.8 Hz, 1H), 5.68 (ddd, *J* = 12.3, 2.8, 1.3 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 7.37–7.41 (m, 1H), 7.70 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.93 (d, *J* = 3.2 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 (CH_3, C-14), 17.5 (CH_3, C-15), 23.8 (CH_2, C-2), 35.1 (CH_2, C-3), 36.0 (CH_2, C-8), 37.9 (CH, C-7), 55.8 (OCH_3), 61.5 (C_q, C-4), 66.5 (CH, C-5), 71.8 (CH, C-9), 81.9 (CH, C-6), 110.9 (CH_{ar}), 120.1 (CH_{ar}), 122.3 (CH, C-1), 122.5 (C_{ar}), 128.8 (C_q, C-11), 131.1 (CH_{ar}), 131.3 (CH_{ar}), 133.9 (CH, C-13), 137.1 (C_q, C-10), 158.1 (C_{ar}), 171.2 (CO, C-12) ppm. IR (ATR diamond): ν = 3490, 2930, 1716, 1599, 1511, 1441, 1199, 1171, 1017, 940, 814, 780, 750, 696 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{27}O_5$ [M + H]+ 371.1850, found 371.1853.

9α-Hydroxy-13-(3-methoxyphenyl)parthenolide (15)

$[\alpha]_D^{20}$ + 208.4 (*c* 1.0, CH_2Cl_2); yield = 60%; m.p. 180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30–1.38 (m, 1H), 1.34 (s, 3H), 1.63–1.67 (m, 1H), 1.66 (s, 3H), 1.92 (s, 1H), 2.20 (ddd, *J* = 12.6, 4.8, 1.9 Hz, 1H), 2.30 (d, *J* = 13.5 Hz, 1H), 2.47–2.61 (m, 2H), 2.87 (d, *J* = 7.6 Hz, 1H), 3.87 (s, 3H), 3.93–3.96 (m, 2H), 4.20 (d, *J* = 4.6 Hz, 1H), 5.71 (ddd, *J* = 12.6, 2.8, 1.3 Hz, 1H), 6.95 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.21 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 2.0 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 (CH_3, C-14), 17.6 (CH_3, C-15), 23.9 (CH_2, C-2), 35.2 (CH_2, C-3), 35.9 (CH_2, C-8), 37.8 (CH, C-7), 55.5 (OCH_3), 61.5 (C_q, C-4), 66.3 (CH, C-5), 71.8 (CH, C-9), 81.9 (CH, C-6), 115.3 (CH_{ar}), 116.0 (CH_{ar}), 122.5 (CH, C-1), 123.3 (CH_{ar}), 129.1 (C_{ar}), 129.5 (CH_{ar}), 134.6 (C_q, C-11), 137.1 (C_q, C-10), 138.4 (CH, C-13), 159.5 (C_{ar}), 171.1 (CO, C-12) ppm. IR (ATR diamond): ν = 3491, 2930, 1716, 1637, 1489, 1475, 1228, 1191, 1172, 1033, 918, 815, 734, 684 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{27}O_5$ [M + H]+ 371.1851, found 371.1853.

9α-Hydroxy-13-(4-methoxyphenyl)parthenolide (16)

$[\alpha]_D^{20}$ + 78.9 (*c* 1.0, CH_2Cl_2); yield = 66%; m.p. 170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31–1.39 (m, 1H), 1.35 (s, 3H), 1.62–1.66 (m, 1H), 1.69 (s, 3H), 1.87 (s, 1H), 2.21 (ddd, *J* = 6.8, 4.6, 1.7 Hz, 1H), 2.31 (d, *J* = 13.6 Hz, 1H), 2.48–2.59 (m, 1H), 2.67 (dd, *J* = 15.3, 5.7 Hz, 1H), 2.87 (d, *J* = 7.6 Hz, 1H), 3.87 (s, 3H), 3.89–3.97 (m, 2H), 4.25 (d, *J* = 4.0 Hz, 1H), 5.72 (dd, *J* = 12.2, 3.8 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 (CH_3, C-14), 17.6 (CH_3, C-15), 23.6 (CH_2, C-2), 34.9 (CH_2, C-3), 35.9 (CH_2, C-8), 37.9 (CH, C-7), 55.4 (OCH_3), 61.5 (C_q, C-4), 66.4 (CH, C-5), 72.2 (CH, C-9), 81.8 (CH, C-6), 113.9 (2 × CH_{ar}), 122.6 (CH, C-1), 125.7 (C_{ar}), 125.8 (C_q, C-11), 133.1 (2 × CH_{ar}), 137.6 (C_q, C-10), 138.3 (CH, C-13), 160.8 (C_{ar}), 171.7 (CO, C-12) ppm. IR (ATR diamond): ν = 3489, 2930, 1716, 1600, 1511, 1457, 1239, 1198, 1057, 814, 752, 695 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{27}O_5$ [M + H]+ 371.1850, found 371.1853.

9α-Hydroxy-13-(4-methylphenyl)parthenolide (17)

$[\alpha]_D^{20}$ + 111.8 (*c* 1.0, CH_2Cl_2); yield = 75%; m.p. 107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30–1.38 (m, 1H), 1.35 (s, 3H), 1.61–1.65 (m, 1H), 1.67 (s, 3H), 1.89 (s, 1H), 2.20 (ddd, *J* = 7.0, 4.7, 1.9 Hz, 1H), 2.30 (d, *J* = 13.6 Hz, 1H), 2.40 (s, 3H), 2.48–2.58 (m, 1H), 2.63 (dd, *J* = 15.2, 5.8 Hz, 1H), 2.87 (d, *J* = 7.6 Hz, 1H), 3.84–4.00 (m, 2H), 4.21 (d, *J* = 5.0 Hz, 1H), 5.71 (ddd, *J* = 12.3, 2.8, 1.2 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 2.5 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 (CH_3, C-14), 17.6 (CH_3, C-15), 21.5 (CH_3-Ph), 23.9 (CH_2, C-2), 34.9 (CH_2, C-3), 35.9 (CH_2, C-8), 37.9 (CH, C-7), 61.5 (C_q, C-4), 66.4 (CH, C-5), 72.1 (CH, C-9), 81.9 (CH, C-6), 122.5 (CH, C-1), 127.4 (C_{ar}), 129.1 (2 × CH_{ar}), 130.3 (C_q, C-11), 131.1 (2 × CH_{ar}), 137.5 (C_q, C-10), 138.6 (CH, C-13), 140.1

(C_{ar}), 171.5 (CO, C-12) ppm. IR (ATR diamond): ν = 3467, 2929, 1746, 1639, 1338, 1197, 1175, 1057, 849, 816, 774, 732 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{27}O_4$ [M + H]+ 355.1901, found 355.1903.

9α-Hydroxy-13-(4-hydroxyphenyl)parthenolide (18)

$[\alpha]_D^{20}$ +180.0 (*c* 1.0, CH_2Cl_2); yield = 65%; m.p. 200 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.26–1.31 (m, 1H), 1.32 (s, 3H), 1.72 (s, 3H), 1.83 (dd, *J* = 15.0, 8.6 Hz, 1H), 2.12 (ddd, *J* = 12.3, 4.9, 2.0 Hz, 1H), 2.24 (d, *J* = 14.2 Hz, 1H), 2.53–2.68 (m, 2H), 2.89 (d, *J* = 8.3 Hz, 1H), 3.92–3.98 (m, 1H), 4.07 (dd, *J* = 8.3, 6.6 Hz, 1H), 4.24 (s, 1H), 4.42 (d, *J* = 2.1 Hz, 1H), 5.82 (ddd, *J* = 12.4, 2.7, 1.3 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 3.0 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 8.87 (s, 1H) ppm. ^{13}C NMR (101 MHz, acetone-d_6) δ 15.5 (CH_3, C-14), 17.0 (CH_3, C-15), 23.6 (CH_2, C-2), 34.4 (CH_2, C-3), 35.8 (CH_2, C-8), 37.8 (CH, C-7), 60.9 (C_q, C-4), 66.1 (CH, C-5), 71.5 (CH, C-9), 81.4 (CH, C-6), 115.2 (2 × CH_{ar}), 122.1 (CH, C-1), 124.8 (C_{ar}), 126.2 (C_q, C-11), 133.6 (2 × CH_{ar}), 136.9 (CH, C-13), 138.0 (C_q, C-10), 158.9 (C_{ar}), 171.2 (CO, C-12) ppm. IR (ATR diamond): ν = 3517, 3287, 2951, 1719, 1651, 1634, 1447, 1330, 1311, 1248, 1225, 1168, 991, 909, 751, 739 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{25}O_5$ [M + H]+ 357.1694, found 357.1696.

9α-Hydroxy-13-(4-aminophenyl)parthenolide (19)

$[\alpha]_D^{20}$ +26.1 (*c* 1.0, CH_2Cl_2); yield = 60%; m.p. 153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31–1.38 (m, 1H), 1.34 (s, 3H), 1.60–1.64 (m, 1H), 1.68 (s, 3H), 2.02 (s, 1H), 2.20 (ddd, *J* = 12.4, 4.6, 1.8 Hz, 1H), 2.30 (d, *J* = 13.4 Hz, 1H), 2.53 (qd, *J* = 13.1, 4.9 Hz, 1H), 2.71 (dd, *J* = 15.2, 5.7 Hz, 1H), 2.86 (d, *J* = 7.8 Hz, 1H), 3.85–3.94 (m, 2H), 4.05 (s, 2H), 4.24 (d, *J* = 4.2 Hz, 1H), 5.71 (ddd, *J* = 12.3, 2.7, 1.2 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 3.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 (CH_3, C-14), 17.6 (CH_3, C-15), 24.0 (CH_2, C-2), 34.9 (CH_2, C-3), 35.9 (CH_2, C-8), 38.0 (CH, C-7), 61.5 (C_q, C-4), 66.5 (CH, C-5), 72.2 (CH, C-9), 81.7 (CH, C-6), 114.4 (2 × CH_{ar}), 122.5 (CH, C-1), 123.2 (C_{ar}), 123.4 (C_q, C-11), 133.3 (2 × CH_{ar}), 137.7 (C_q, C-10), 139.1 (CH, C-13), 148.3 (C_{ar}), 172.1(CO, C-12) ppm. IR (ATR diamond): ν = 3365, 2930, 1720, 1622, 1596, 1339, 1199, 1170, 1122, 906, 870, 779, 728 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{26}NO_4$ [M + H]+ 356.1851, found 356.1856.

General procedure to prepare compounds 20–23

Acetic anhydride (0.65 mmol) at 0 °C was added to a solution of 9α-hydroxy-13-arylparthenolide (0.5 mmol) in a dry mixture of CH_2Cl_2 and pyridine (9 : 1) (20 mL). The solution was stirred at room temperature for 12 h and poured into saturated aqueous NH_4Cl (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by column chromatography (PE-EtOAc, 7 : 3) provided compounds **20**–**23**.

9α-Acetoxy-13-phenylparthenolide (20)

$[\alpha]_D^{20}$ +34.7 (*c* 1.0, CH_2Cl_2); yield = 80%; m.p. 237 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27–1.37 (m, 1H), 1.35 (s, 3H), 1.73 (s, 3H), 1.74–1.78 (m, 1H), 2.21 (ddd, *J* = 12.9, 5.0, 1.9 Hz, 1H), 2.27 (d, *J* = 13.6 Hz, 1H), 2.35 (s, 3H), 2.44–2.57 (m, 2H), 2.88 (d, *J* = 8.1 Hz, 1H), 3.82–3.87 (m, 1H), 3.98–4.01 (m, 1H), 5.08 (d, *J* = 5.2Hz, 1H), 5.43 (dd, *J* = 11.8, 3.4 Hz, 1H), 7.37–7.40 (m, 3H), 7.53–7.55 (m, 2H), 7.73 (d, *J* = 3.0 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 (CH_3, C-14), 17.5 (CH_3, C-15), 21.3 (CH_3CO_2R), 23.9 (CH_2, C-2), 33.1 (CH_2, C-3), 35.8 (CH_2, C-8), 39.5 (CH, C-7), 61.5 (C_q, C-4), 66.3 (CH, C-5), 73.6 (CH, C-9), 81.6 (CH, C-6), 122.9 (CH, C-1), 128.0 (C_{ar}), 128.3 (2 × CH_{ar}), 129.9 (CH_{ar}), 130.1 (2 × CH_{ar}), 133.1 (C_q, C-11), 133.4 (C_q, C-10), 138.9 (CH, C-13), 169.0 (CO), 170.7 (CO, C-12) ppm. IR (ATR diamond): ν = 2936, 1742, 1720, 1644, 1297, 1228, 1186, 905, 765, 725 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{27}O_5$ [M + H]+ 383.1853, found 383.1853.

9α-Acetoxy-13-(2-fluorophenyl)parthenolide (21)

$[\alpha]_D^{20}$ +27.3 (*c* 1.0, CH_2Cl_2); yield = 83%; m.p. 221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27–1.34 (m, 1H), 1.36 (s, 3H), 1.71 (s, 3H), 1.75–1.82 (m, 1H), 2.19–2.26 (m, 2H), 2.30 (s, 3H), 2.36 (dd, *J* = 15.6, 5.7 Hz, 1H), 2.49 (qd, *J* = 13.1, 4.9 Hz, 1H), 2.89 (d, *J* = 8.1 Hz, 1H), 3.73–3.78 (m, 1H), 3.96–4.00 (m, 1H), 5.05 (d, *J* = 5.3 Hz, 1H), 5.45 (dd, *J* = 12.2, 3.8 Hz, 1H), 7.09–7.18 (m, 2H), 7.41 (td, *J* = 7.5, 1.4 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 3.0 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 (CH_3, C-14), 17.5 (CH_3, C-15), 21.3 (CH_3CO_2R), 23.9 (CH_2, C-2), 33.2 (CH_2, C-3), 35.8 (CH_2, C-8), 40.0 (CH, C-7), 61.5 (C_q, C-4), 66.1 (CH, C-5), 73.1 (CH, C-9), 81.4 (CH, C-6), 116.0 (d, *J* = 21.4 Hz, CH_{ar}), 121.4 (d, *J* = 14.3 Hz, C_{ar}), 123.1 (CH, C-1), 123.8 (d, *J* = 3.6 Hz, CH_{ar}), 130.4 (d, *J* = 2.6 Hz, CH_{ar}), 131.0 (C_q, C-11), 131.5 (d, *J* = 3.0 Hz, CH_{ar}), 131.7 (d, *J* = 8 Hz, CH, C-13), 133.1(C_q, C-10), 160.4 (d, *J* = 252.1 Hz, C_{ar}), 169.1 (CO), 170.0 (CO, C-12) ppm. IR (ATR diamond): ν = 2934, 1743, 1722, 1647, 1390, 1274, 1227, 1186, 1163, 1127, 905, 723, 694 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{26}FO_5$ [M + H]+ 401.1759, found 401.1759.

9α-Acetoxy-13-(2-methoxyphenyl)parthenolide (22)

$[\alpha]_D^{20}$ +41.3 (*c* 1.0, CH_2Cl_2); yield = 70%; m.p. 218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30–1.36 (m, 1H), 1.34 (s, 3H), 1.69–1.75 (m, 1H), 1.71 (s, 3H), 2.18–2.28 m, 2H), 2.31 (s, 3H), 2.43–2.55 (m, 2H), 2.87 (d, *J* = 8.2 Hz, 1H), 3.78–3.83 (m, 1H), 3.89 (s, 3H), 3.94–3.98 (m, 1H), 5.03 (d, *J* = 5.3 Hz, 1H), 5.41 (dd, *J* = 11.9, 3.3 Hz, 1H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.97 (d, *J* = 3.0 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 (CH_3, C-14), 17.5 (CH_3, C-15), 21.3 (CH_3CO_2R), 23.9 (CH_2, C-2), 32.9 (CH_2, C-3), 35.8 (CH_2, C-8), 39.4 (CH, C-7), 55.6 (OCH_3), 61.5 (C_q, C-4), 66.4 (CH, C-5), 73.5 (CH, C-9), 81.5 (CH, C-6), 110.9 (CH_{ar}), 119.5 (CH_{ar}), 122.2 (C_{ar}), 122.6 (CH, C-1), 127.7 (C_q, C-11), 129.7 (CH_{ar}), 131.6 (CH_{ar}), 133.5 (C_q, C-10), 134.5 (CH, C-13), 158.3 (C_{ar}), 169.0 (CO), 170.7 (CO, C-12) ppm. IR (ATR diamond): ν = 2995, 1748, 1728, 1578, 1391, 1372, 1355, 1240, 1227, 1099, 1066, 854, 812, 736, 703 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{29}O_6$ [M + H]+ 413.1958, found 413.1958.

9α-Acetoxy-13-(3-methoxyphenyl)parthenolide (23)

$[\alpha]_D^{20}$ +18.7 (*c* 1.0, CH_2Cl_2); yield = 75%; m.p. 203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29–1.36 (m, 1H), 1.35 (s, 3H), 1.69–1.75 (m, 1H), 1.72 (s, 3H), 2.18–2.28 (m, 2H), 2.34 (s, 3H), 2.43–2.55 (m, 1H), 2.60 (dd, *J* = 15.5, 5.8 Hz, 1H), 2.88 (d, *J* = 8.1 Hz, 1H), 3.81–3.85 (m, 1H), 3.83 (s, 3H), 3.96–4.00 (m, 1H), 5.09 (d, *J* = 5.3 Hz, 1H), 5.42 (ddd, *J* = 12.3, 2.7, 1.1 Hz, 1H), 6.92 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.09–7.11 (m, 2H), 7.31 (t, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 3.0 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 (CH_3, C-14), 17.5 (CH_3, C-15), 21.2 (CH_3CO_2R), 23.9 (CH_2, C-2), 32.8 (CH_2, C-3), 35.8 (CH_2, C-8), 39.5 (CH, C-7), 55.2 (OCH_3), 61.5 (C_q, C-4), 66.2 (CH, C-5), 73.4 (CH, C-9), 81.6 (CH, C-6), 113.6 (CH_{ar}), 117.2 (CH_{ar}), 122.6 (CH, C-1), 122.7 (CH_{ar}), 128.4 (C_{ar}), 129.4 (CH_{ar}), 133.5 (C_q, C-11), 134.3 (C_q, C-10), 138.7 (CH, C-13), 159.5 (C_{ar}), 169.4 (CO), 170.7 (CO, C-12) ppm IR (ATR diamond): ν = 2935,

1742, 1645, 1612, 1297, 1227, 1886, 1163, 1127, 1020, 905, 785, 727, 676 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{29}O_6$ [M + H]+ 413.57, found 413.1958.

Determination of in vitro cytotoxic activity

Cancer cell lines (**Table 1**) were commercially obtained from the Cell Lines Service of GmbH. Cytotoxic activity was determined on four cancer cell lines using a colorimetric MTT (thiazolyl blue tetrazolium bromide) assay. Human skin melanoma SK-Mel-28 and human brain glioma HS-683 were grown in DMEM supplemented with 4.5 g/L glucose, L-glutamine, and 10% FBS. The human lung carcinoma cell line A549 was grown in DMEM : Ham's F12 (1 : 1) supplemented with L-glutamine and 5% FBS and human breast adenomacarcinoma MCF-7 in EMEM supplemented with L-glutamine, sodium pyruvate, NEAA, and 10% FBS. The MTT assay is based on the reduction of the yellow product MTT to purple-blue formazan by mitochondrial dehydrogenase of metabolically active cells. The number of living cells after incubation in the presence (or absence, control) of the tested molecule is directly proportional to the blue color that was measured by spectrophotometry. Briefly, cells were seeded (200 µL of a 5×10^4 cells/mL suspension) in 96-well culture plates (TPP) and incubated for 24 h. Each compound (starting from DMSO solutions) was assessed in serial dilution (four concentrations) in 6 replicates of 2–3 independent experiments (n = 2–3) and incubated for 72 h. Thereafter, MTT (5 mg/mL solution in PBS) was added to each well (10% v/v) and cells were further incubated for 4 h. Then, after removing the culture medium, the blue crystals were dissolved in 100 µL SDS-acidic-isopropanol solution (0.5% SDS; 80 mM HCl) and absorbance measured at 540 nm using a 620 nm reference. Absorbance of the serial dilution of each cell line treated under the same conditions, but without the tested compounds, was measured to generate a standard curve allowing cell number determination. Individual IC_{50} s (defined as the concentration reducing cell number by 50%) were calculated by using linear regression equation (as given by Excel software) of the curve obtained in the presence of four concentrations of compound. IC_{50} values are the geometric mean from two to three independent experiments. 95% Confidence limits were determined using the Excel confidence interval function.

Supporting information

^1H and ^{13}C NMR spectra of compound **3**–**23** are available as Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

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