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SYNTHESIS OF NEW BETULONIC AND OLEANONIC ACID AMIDES

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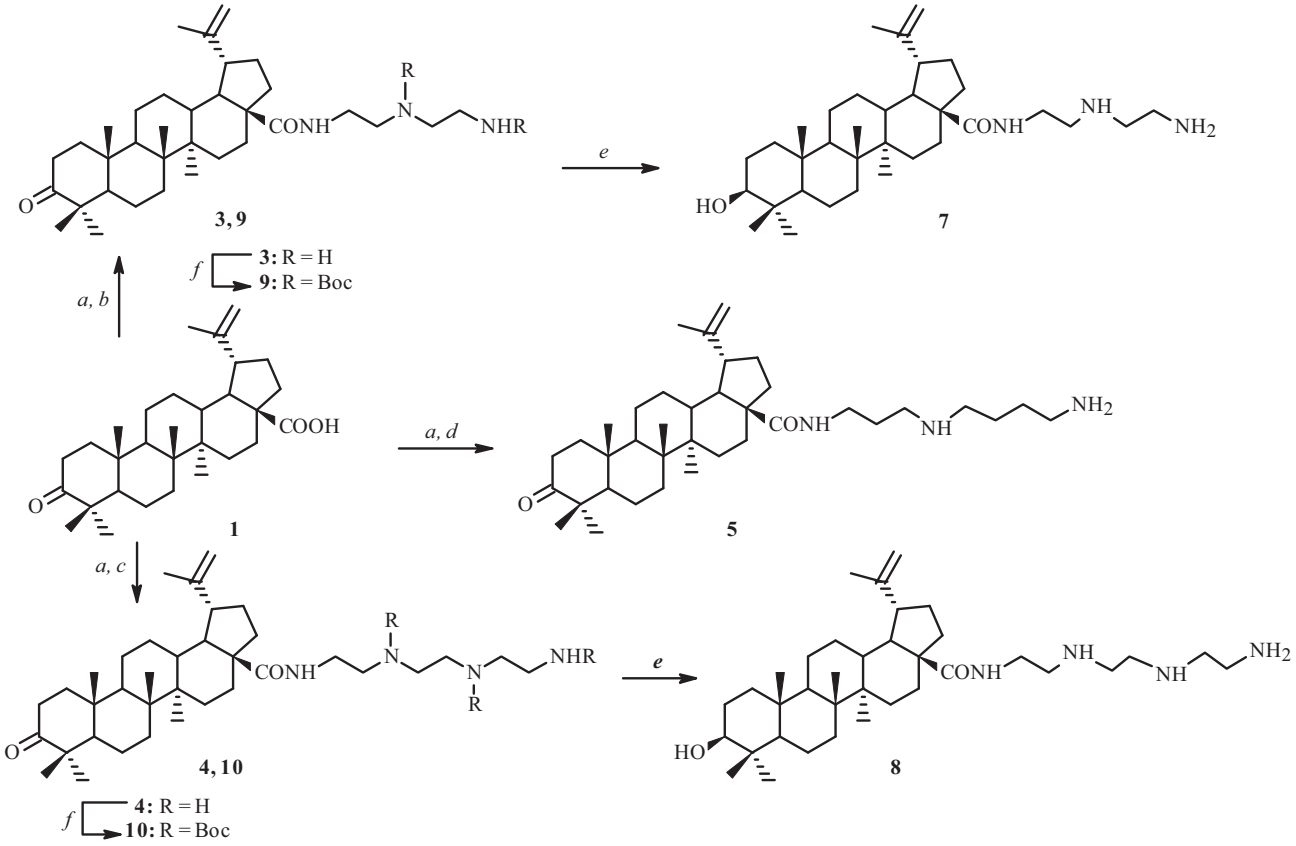
Amides of betulonic and oleanonic acids with diethylenetriamine, triethylenetetramine, and spermidine were synthesized. Antitumor activity in vitro *was not found for the conjugate of betulonic acid with diethylenetriamine.*

Keywords: triterpenoids, betulonic acid, oleanolic acid, polyamines, amides, antitumor activity.

Triterpene acids with long O- and N-containing side chains have shown promise for developing antiviral and antitumor agents. Thus, a dipeptide of betulonic acid with a phenylalanine unit affects the early stages of the viral reproduction cycle, is highly active against Herpes simplex virus, and has immunostimulating activity greater than that of Freund's incomplete adjuvant [1, 2].



a. $(COCl)_2$, $CHCl_3$, 2 h; *b*. $NH_2(CH_2)_2NH(CH_2)_2NH_2$, Et_3N, $CHCl_3$, 60°C, 4 h; *c*. $NH_2(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH_2$, Et_3N, $CHCl_3$, 60°C, 5 h; *d*. $NH_2(CH_2)_3NH(CH_2)_4NH_2$, Et_3N, $CHCl_3$, 60°C, 6 h; *e*. $NaBH_4$, isopropanol, 2 h; *f*. Boc_2O, CH_2Cl_2, 5 h.

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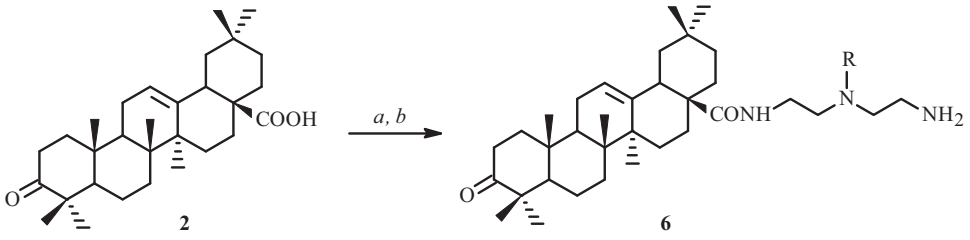
TABLE 1. Antitumor Activity *in vitro* of **3** (10^{-5} M) Against 60 Human Cancer Cell Lines

Cell line	Percent growth	Cell line	Percent growth
Lung cancer		Leukemia	
A549/ATCC	95.49	CCRF-CEM	100.49
EKVX	99.41	HL-60(TB)	100.10
HOP-62	107.24	K-562	83.89
NCI-H226	109.94	MOLT-4	100.28
NCI-H322M	104.33	RPMI-8226	80.10
NCI-H23	108.73	SR	63.11
NCI-H460	99.93	Kidney cancer	
NCI-H522	111.44	786-0	108.91
HOP-92	88.03	A498	96.12
Colon cancer		ACHN	133.93
COLO 205	120.27	CAKI-1	107.47
HCC-2998	112.46	RXF 393	127.77
HCT-116	96.23	SN12C	79.65
HCT-15	129.27	TK-10	108.91
HT29	104.82	UO-31	96.12
KM12	89.75	Melanoma	
SW-620	101.98	LOX IMVI	107.25
Breast cancer		MALME-3M	117.89
MCF7	96.50	M14	111.81
MDA-MB-231/ATCC	103.94	MDA-MB-435	103.65
HS 578T	115.48	SK-MEL-2	134.40
BT-549	119.07	SK-MEL-28	114.64
T-47D	114.07	SK-MEL-5	110.06
MDA-MB-468	108.67	UACC-257	122.58
Ovarian cancer		UACC-62	93.29
IGROV1	110.41	Prostate cancer	
OVCAR-3	93.33	PC-3	82.59
OVCAR-4	109.04	DU-145	105.99
OVCAR-5	108.73	CNS cancer	
OVCAR-8	115.84	SF-268	84.85
NCI/ADR-RES	111.69	SF-295	96.34
SK-OV-3	110.84	SF-539	94.27
		SNB-19	94.56
		SNB-75	93.55
		U251	101.00



2 **6**

a. $(COCl)_2$, $CHCl_3$, 2 h; *b*. $NH_2(CH_2)_2NH(CH_2)_2NH_2$, Et_3N, $CHCl_3$, 60°C, 4 h.

The activities of esters of acetylbetulinic acid with 2,3-dihydroxy-2-hydroxymethylpropane, 2-amino-3-hydroxy-2-hydroxymethylpropane, and *N*-(1,1-*bis*(hydroxymethyl)-2-hydroxyethyl)formamide are seven times greater than that of betulinic acid against HTB-92 liposarcoma and 518A2 melanoma. Furthermore, they are also active against HIV-1 [3]. Derivatives of oleanolic and ursolic acids exhibit antitumor activity against leukemia and HT-29 colon cells [4, 5]. 2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) and its methyl ester and imidazolide are active against leukemia, multiple myeloma, breast, lung, and osteosarcoma cells and are undergoing Phase I clinical trials [6, 7].

Stepwise elaboration of the side chain is usually used to synthesize triterpenoids with polyamine substituents. However, such structures can be synthesized by introducing commercially available alkanepolyamines. Herein we report the synthesis of amides of betulonic (**1**) and oleanonic (**2**) acids obtained via reaction of their acid chlorides with diethylenetriamine, triethylenetetramine, and spermidine. Compounds **3**–**6** were synthesized in 48–54% yields after purification by column chromatography. Their structures were confirmed by NMR spectroscopy. Thus, the C-28 resonance in ^{13}C NMR spectra was located at δ 176 ppm. The H-28 resonance in PMR spectra appeared at δ 6.26–6.41 ppm as a multiplet. Resonances of methylene protons introduced into the structure of the alkanepolyamines gave multiplets at δ 2.74–3.62.

Derivatives of betulinic acid **7** and **8** were synthesized via reduction of the C-3 ketone of amides **3** and **4** by $NaBH_4$. Considering the anticancer activity of betulonic acid amide that contains an *N*-Boc-protected lysine [8], we prepared *N*-Boc-amides **9** and **10**. Strong singlets in the PMR spectra of these compounds at 1.28–1.52 ppm corresponded to the *tert*-butoxycarbonyl protons.

The antitumor activity *in vitro* (cytotoxicity) of **3** was studied at the National Cancer Institute (USA) against 60 cell lines of nine different human tumors (lung, colon, CNS, ovarian, kidney, prostate, brain, leukemia, and melanoma) by the literature method [9–12]. Preliminary testing of the activity was carried out in cell cultivation medium at a final concentration of 10^{-5} M for 48 h, after which the growth of the treated cells was estimated compared with that of untreated control cells. Table 1 presents the percent growth of treated cells compared with control cells (negative values correspond to cell death). It can be seen that 3-oxo-28-(diethylenetriamino)-carbonyl-lup-20(29)-ene (**3**) did not exhibit antitumor activity.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and CD_3OD with TMS internal standard on a Bruker AM-300 spectrometer (Germany, 300 and 75.5 MHz, respectively, δ, ppm, SSCC, Hz). Melting points were determined on a Boetius microstage. Optical absorption was measured on a Perkin–Elmer 241 MC polarimeter (Germany) in a 1-dm tube. TLC was performed on Sorbfil plates (ZAO Sorbpolimer, Russia) using $CHCl_3$:EtOAc (40:1). Compounds were detected by H_2SO_4 solution (10%) with subsequent heating at 100–120°C for 2–3 min. We used oleanolic acid, diethylenetriamine, triethylenetetramine, and spermidine (Aldrich Chemical Co.). Betulonic acid (**1**) was synthesized from betulin [13]. Oleanolic acid was oxidized to oleanonic acid (**2**) by Jones reagent in acetone as before [14]. Betulonic and oleanonic acid chlorides were prepared by the standard method [15] by reaction with oxalylchloride in $CHCl_3$.

Preparation of 3–5. A solution of betulonic acid chloride (0.46 g, 1 mmol) in dry $CHCl_3$ (30 mL) was treated with diethylenetriamine, triethylenetetramine, or spermidine (1 mmol) and dropwise with Et_3N (3 mL); refluxed (TLC monitoring); washed with HCl solution (5%, 2 × 50 mL) and H_2O (50 mL); and dried over $CaCl_2$. The solvent was removed in vacuo. The solid was chromatographed over a column of Al_2O_3 with elution by benzene.

***N*-3a-[2-(2-Aminoethylamino)ethyl]-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-9-oxoperhydrocyclopenta[*a*]chrysen-3a-carboxamide (3).** Yield 0.27 g (54%), R_f 0.32, mp 158–160°C, $[\alpha]_D^{20}$ +21° (*c* 0.23, $CHCl_3$). $C_{34}H_{57}N_3O_2$ (MW 539.842).

PMR spectrum ($CDCl_3$, δ, ppm): 0.86, 0.92, 0.96, 1.04, 1.13 (15H, 5s, $5CH_3$), 1.10–2.18 (24H, m, CH_2, CH, NH, NH_2), 1.69 (3H, s, H-30), 2.35–2.56 (3H, m, H-13, H-16), 2.74–2.89 (6H, m, H-2′, H-3′, H-4′), 3.03–3.17 (1H, m, H-19), 3.33–3.47 (2H, m, H-1′), 4.62 and 4.75 (1H each, both br., H-29), 6.26–6.37 (1H, m, CONH).

^{13}C NMR spectrum (δ, ppm): 14.5, 15.8, 15.9, 16.1, 19.4, 19.6, 20.9, 21.4, 25.6, 26.6, 27.4, 29.4, 30.9, 33.4, 33.7, 34.0, 36.9, 37.8, 38.3, 38.7, 39.6, 40.7, 42.5, 46.6, 47.2, 49.3, 50.0, 50.1, 55.0, 55.7, 109.4 (C-29), 150.7 (C-20), 176.7 (CONH), 217.7 (C-3).

***N*-3a-2-[2-(2-Aminoethylamino)ethylamino]ethyl-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-9-oxoperhydrocyclopenta[*a*]chrysen-3a-carboxamide (4).** Yield 0.24 g (48%), R_f 0.34, mp 173–175°C, $[\alpha]_D^{20}$ +19° (*c* 0.35, $CHCl_3$). $C_{36}H_{62}N_4O_2$ (MW 582.911).

PMR spectrum ($CDCl_3$, δ, ppm): 0.86, 0.92, 0.96, 1.04, 1.13 (15H, 5s, $5CH_3$), 1.10–2.18 (25H, m, CH_2, CH, 2NH, NH_2), 1.69 (3H, s, H-30), 2.35–2.56 (3H, m, H-13, H-16), 2.71–2.85 (4H, m, H-3′, H-4′), 2.89–2.98 (4H, m, H-2′, H-5′), 3.03–3.17 (1H, m, H-19), 3.25–3.62 (4H, m, H-1′, H-6′), 4.62 and 4.75 (1H each, both br., H-29), 6.28–6.41 (1H, m, CONH).

^{13}C NMR spectrum (δ, ppm): 14.6, 15.9, 16.0, 19.4, 19.7, 21.0, 21.5, 25.7, 26.6, 29.3, 29.4, 30.9, 33.7, 34.1, 36.9, 37.8, 38.4, 39.6, 40.2, 40.5, 40.7, 42.5, 45.7, 46.7, 47.3, 47.4, 49.0, 50.0, 53.1, 53.9, 55.0, 55.7, 109.4 (C-29), 150.9 (C-20), 176.6 (CONH), 218.0 (C-3).

***N*-3a-[3-(4-Aminobutylamino)propyl]-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-9-oxoperhydrocyclopenta[*a*]chrysen-3a-carboxamide (5).** Yield 0.3 g (52%), R_f 0.28, mp 154–157°C, $[\alpha]_D^{20}$ +29° (*c* 0.6, $CHCl_3$). $C_{37}H_{63}N_3O_2$ (MW 581.923).

PMR spectrum ($CDCl_3$, δ, ppm): 0.86, 0.92, 0.96, 1.04, 1.13 (15H, 5s, $5CH_3$), 1.10–2.18 (30H, m, CH_2, CH, H-2′, H-3′, H-6′, NH, NH_2), 1.69 (3H, s, H-30), 2.35–2.56 (3H, m, H-13, H-16), 2.74–2.89 (6H, m, H-4′, H-5′, H-7′), 3.03–3.17 (1H, m, H-19), 3.33–3.47 (2H, m, H-1′), 4.62 and 4.75 (1H each, both br., H-29), 6.26-6.37 (1H, m, CONH).

^{13}C NMR spectrum (δ, ppm): 14.4, 15.1, 15.9, 16.0, 19.3, 19.5, 20.9, 21.4, 25.5, 26.1, 26.5, 27.2, 29.3, 29.4, 30.8, 33.6, 34.0, 36.8, 36.9, 37.0, 37.4, 37.6, 38.3, 38.6, 39.5, 40.6, 42.4, 46.6, 47.2, 48.9, 49.9, 50.0, 55.4, 109.3 (C-29), 150.7 (C-20), 176.2 (CONH), 217.9 (C-3).

***N*-5-[2-(2-Aminoethylamino)ethyl]-1,2,8,8,15,19,19-heptamethyl-18-oxopentacyclo[12.8.0.0^{2,11}.0^{5,10}.0^{15,20}]-docos-11-en-5-carboxamide (6).** A solution of oleanonic acid chloride (0.46 g, 1 mmol) in dry $CHCl_3$ (30 mL) was treated with diethylenetriamine (1 mmol) and dropwise with Et_3N (3 mL), refluxed (TLC monitoring), washed with HCl solution (5%, 2 × 50 mL) and H_2O (50 mL), and dried over $CaCl_2$. The solvent was removed in vacuo. The solid was chromatographed over a column of Al_2O_3 with elution by benzene. Yield 0.26 g (48%), R_f 0.39, mp 125–128°C, $[\alpha]_D^{20}$ +67° (*c* 0.48, $CHCl_3$). $C_{34}H_{57}N_3O_2$ (MW 539.842).

PMR spectrum ($CDCl_3$, δ, ppm): 0.78, 0.89, 0.93, 1.01, 1.03, 1.11, 1.14 (21H, 7s, $7CH_3$), 1.20–2.12 (25H, m, CH_2, CH, NH, NH_2), 2.76–2.87 (7H, m, H-11, H-2′, H-3′, H-4′), 3.12–3.22 (2H, m, H-1′), 5.39–5.52 (1H, br., H-12), 5.89–5.98 (1H, m, CONH).

^{13}C NMR spectrum (δ, ppm): 14.0, 15.0, 16.8, 19.5, 21.2, 22.5, 23.4, 23.7, 25.4, 25.6, 26.2, 27.1, 29.2, 29.6, 30.5, 31.7, 32.9, 33.8, 34.0, 36.1, 36.6, 38.9, 39.2, 41.1, 41.7, 46.1, 46.4, 46.7, 47.4, 55.1, 122.4 (C-12), 143.9 (C-14), 177.8 (CONH), 215.9 (C-3).

Synthesis of 7 and 8. A solution of **3** or **4** (1 mmol) in isopropanol (20 mL) was stirred, treated over 10 min with $NaBH_4$ (50 mg, 1.3 mmol), stored for 2 h, and diluted with HCl solution (30 mL, 10%). The solid was filtered off, washed with H_2O, dried, and recrystallized from MeOH.

***N*-3a-[2-(2-Aminoethylamino)ethyl]-9-hydroxy-1-isopropenyl-5a,5b,8,8,11a-pentamethylperhydrocyclopenta[*a*]chrysen-3a-carboxamide (7).** Yield 0.49 g (92%), R_f 0.27, mp 213–215°C, $[\alpha]_D^{20}$ +13° (*c* 0. 35, CH_3OH). $C_{34}H_{59}N_3O_2$ (MW 541.858).

PMR spectrum (CD_3OD, δ, ppm): 0.86, 0.92, 0.96, 1.04, 1.13 (15H, 5s, $5CH_3$), 1.10–2.03 (25H, m, CH_2, CH, NH, NH_2), 1.69 (3H, s, H-30), 2.35–2.56 (3H, m, H-13, H-16), 2.68–2.81 (6H, m, H-2′, H-3′, H-4′), 3.03–3.17 (1H, m, H-19), 3.23–3.47 (3H, m, H-3, H-1′), 4.62 and 4.75 (1H each, both br., H-29), 6.03–6.14 (1H, m, CONH).

^{13}C NMR spectrum (δ, ppm): 14.6, 15.3, 16.1, 18.2, 19.4, 19.6, 20.9, 21.4, 25.6, 27.4, 27.9, 29.4, 30.9, 33.7, 34.4, 36.9, 37.1, 37.4, 37.7, 38.4, 38.8, 40.7, 42.4, 46.7, 48.9, 49.3, 50.1, 50.6, 55.3, 55.6, 78.9 (C-3), 109.4 (C-29), 150.7 (C-20), 176.7 (CONH).

***N*-3a-2-[2-(2-Aminoethylamino)ethylamino]ethyl-9-hydroxy-1-isopropenyl-5a,5b,8,8,11a-pentamethylperhydrocyclopenta[*a*]chrysen-3a-carboxamide (8).** Yield 0.49 g (92%), R_f 0.25, mp 221–223°C, $[\alpha]_D^{20}$ +5° (*c* 1.25, CH_3OH). $C_{36}H_{64}N_4O_2$ (MW 584.926).

PMR spectrum (CD_3OD, δ, ppm): 0.86, 0.92, 0.96, 1.04, 1.13 (15H, 5s, $5CH_3$), 1.10–2.18 (26H, m, CH_2, CH, 2NH, NH_2), 1.69 (3H, s, H-30), 2.35–2.56 (3H, m, H-13, H-16), 2.71–2.85 (4H, m, H-3′, H-4′), 2.89–2.98 (4H, m, H-2′, H-5′), 3.03–3.17 (1H, m, H-19), 3.25–3.62 (5H, m, H-3, H-1′, H-6′), 4.62 and 4.75 (1H each, both br., H-29), 6.28–6.41 (1H, m, CONH).

^{13}C NMR spectrum (δ, ppm): 14.6, 15.9, 16.0, 19.4, 19.7, 21.0, 21.5, 25.7, 26.6, 29.3, 29.4, 30.9, 33.7, 34.1, 36.9, 37.8, 38.4, 39.6, 40.2, 40.5, 40.7, 42.5, 45.7, 46.7, 47.3, 47.4, 49.0, 50.0, 53.1, 53.9, 55.0, 55.7, 78.8 (C-3), 109.4 (C-29), 150.9 (C-20), 176.6 (CONH).

Synthesis of 9 and 10. A solution of **3** or **4** (1 mmol) in CH_2Cl_2 (20 mL) was treated with di-*tert*-butylbicarbonate (349 mg, 1.59 mmol or 465 mg, 2.12 mmol), stirred at room temperature for 12 h, and evaporated in vacuo. The solid was chromatographed over Al_2O_3 with elution by $CHCl_3$.

***N*-3a-[2-*tert*-Butylformyl-(2-*tert*-butylformylaminoethyl)aminoethyl]-1-isopropenyl-5b,8,8,11a-tetramethyl-9-oxoperhydrocyclopenta[*a*]chrysen-3a-carboxamide (9).** Yield 0.32 g (60%), R_f 0.80, mp 124–127°C, $[\alpha]_D^{20}$ +21° (*c* 0.04, $CHCl_3$). $C_{44}H_{73}N_3O_6$ (MW 740.075).

PMR spectrum ($CDCl_3$, δ, ppm): 0.86, 0.92, 0.96, 1.04, 1.13 (15H, 5s, $5CH_3$), 1.20–2.00 (21H, m, CH_2, CH), 1.48 (9H, s, CH_3), 1.52 (9H, s, CH_3), 1.69 (3H, s, H-30), 2.35–2.56 (3H, m, H-13, H-16), 3.03–3.17 (1H, m, H-19), 3.22–3.48 (8H, m, H-2′, H-3′, H-4′, H-5′), 4.62 and 4.75 (1H each, br., H-29), 5.91–6.09 (1H, m, NH-6′), 6.48–6.59 (1H, m, CONH).

^{13}C NMR spectrum (δ, ppm): 14.4, 15.8, 15.9, 19.4, 19.5, 20.9, 21.4, 23.5, 25.5, 26.5 ($3CH_3$), 26.7 ($3CH_3$), 27.3, 29.4, 30.8, 31.1, 33.4, 33.7, 34.0, 36.8, 37.6, 38.2, 39.5, 40.6, 42.4, 46.5, 47.2, 49.9, 50.0, 54.6, 54.7, 54.9, 55.4, 80.6, 85.0, 109.3 (C-29), 146.7, 150.8 (C-20), 156.7, 176.6 (CONH), 217.8 (C-3).

***N*-3a-2-*tert*-Butylformyl-[2-*tert*-butylformyl(2-*tert*-butylformylaminoethyl)aminoethyl]aminoethyl-1-isopropenyl-5b,8,8,11a-tetramethyl-9-oxoperhydrocyclopenta[*a*]chrysen-3a-carboxamide (10).** Yield 0.37 g (64%), R_f 0.79, mp 174–176°C, $[\alpha]_D^{20}$ +20° (*c* 0.67, $CHCl_3$). $C_{51}H_{86}N_4O_8$ (MW 883.259).

PMR spectrum ($CDCl_3$, δ, ppm): 0.86, 0.92, 0.96, 1.04, 1.13 (15H, 5s, $5CH_3$), 1.20–2.00 (21H, m, CH_2, CH), 1.28 (9H, s, $3CH_3$), 1.35 (9H, s, $3CH_3$), 1.41 (9H, s, $3CH_3$), 1.69 (3H, s, CH_3), 2.35–2.56 (3H, m, H-13, H-16), 2.92–3.02 (4H, m, H-3′, H-6′), 3.03–3.17 (5H, m, H-19, H-4′, H-5′), 3.22–3.48 (4H, m, H-2′, H-7′), 4.58 and 4.75 (1H each, br., H-29), 5.90–6.07 (1H, m, NH-9′), 6.48–6.59 (1H, m, CONH).

^{13}C NMR spectrum (δ, ppm): 14.5, 15.9, 16.0, 19.4, 19.6, 21.0, 21.4, 23.6, 25.6, 26.6 ($3CH_3$), 26.7 ($3CH_3$), 26.8 ($3CH_3$), 28.4, 29.4, 30.9, 33.4, 33.7, 34.1, 36.9, 37.7, 38.3, 39.6, 40.7, 42.3, 45.4, 46.6, 47.3, 49.9, 50.0, 54.3, 54.5, 54.7, 54.9, 55.4, 55.7, 80.6, 80.7, 84.6, 109.3, 150.0, 150.9 (C-20), 156.4, 156.7, 176.7 (CONH), 218.0 (C-3).

The procedure for testing the antitumor activity *in vitro* of **3** is given at the website www.dtp.nci.nih.gov.

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