Synthesis and Preliminary Biological Studies of Novel Retinamide Derivatives

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We have described the synthesis and biological activity of novel retinamide derivatives. The retinamide derivatives were synthesized by introducing functional side chains into the 4-hydroxy group of 4-HPR. The activities could be dependent on the side chain length, functional group, and hetero atom. The antiproliferative potential of the derivatives was assessed by MTT assay in HCT116 colon cancer cell lines.

Key Words : 4-HPR, Retinoid, Derivatives, Side chain, Biological studies

Introduction

Retinoids are natural and synthetic analogues of vitamin A that are involved in the regulation of several biological functions such as cellular differentiation and proliferation. Clinically, retinoids are useful for the treatment of skin disorders and cancer[1] and are currently being investigated in several other therapeutic areas, including arthritis,[2] dyslipidemias,[3] and the prevention of HIV induced lymphopenia.[4]

All-*trans* retinoic acid (RA) and its amide derivative, *N*-(4-hydroxyphenyl)retinamide (4-HPR) were synthesized years ago and found to be effective against various skin diseases and are now being considered as potential drugs for treatment and prevention of several cancers.[5,6] Though 4-HPR is derived from the natural retinoid, retinoic acid, it is less toxic and substantially less teratogenic than RA.[7] Additionally, the lower toxicity of retinamide has led to its experimental use in animal studies as an antitumor agent[8] and in clinical trials as a chemopreventive agent for breast cancer.[9] 4-HPR displays antiproliferative effects *in vitro* against human breast carcinoma cells[5] and induces apoptosis in the hemopoietic cell line.[10] A recent study suggests that 4-HPR is a highly selective activator of the retinoic acid receptor γ (RAR γ),[9] inhibits AP-1 activity, and induces apoptosis in ovarian cancer cells.[11] Also it has been reported that some 4-HPR derivatives show greater efficacy and less toxicity than original 4-HPR when tested in a culture of breast carcinoma cells.[12] Furthermore, the chemopreventive potential of 4-HPR has been determined against the development and growth of 7,12-dimethylbenzanthracene (DMBA)-induced rat mammary tumor.[13]

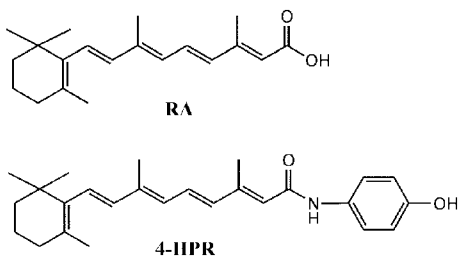


Figure 1.

Results and Discussion

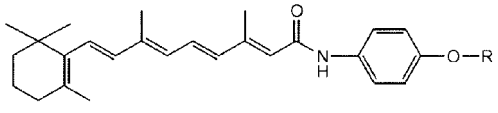
In the present study, we describe the synthesis and biological activity of the retinamide derivatives. The derivatives were synthesized by introducing functional side chains into the 4-hydroxy group of HPR (Figure 2). The antiproliferative potential of the derivatives was determined by MTT in HCT116 colon cancer cell lines.

Various conjugates of 4-HPR have been prepared in two steps as described in Schemes 1 and 2. The preparation of 4-HPR derivatives (Figure 2) consisted of the general *O*-acylation of 4-HPR with various alkanoic acids, sulfonyl chlorides and phosphoryl chlorides.

As shown in Scheme 1, all-*trans* retinoic acid (RA) was converted into an acid chloride derivative using $SOCl_2$ and dimethylformamide (DMF), and then coupled with *p*-aminophenol to obtain 4-HPR by a procedure recently described.[14,15]

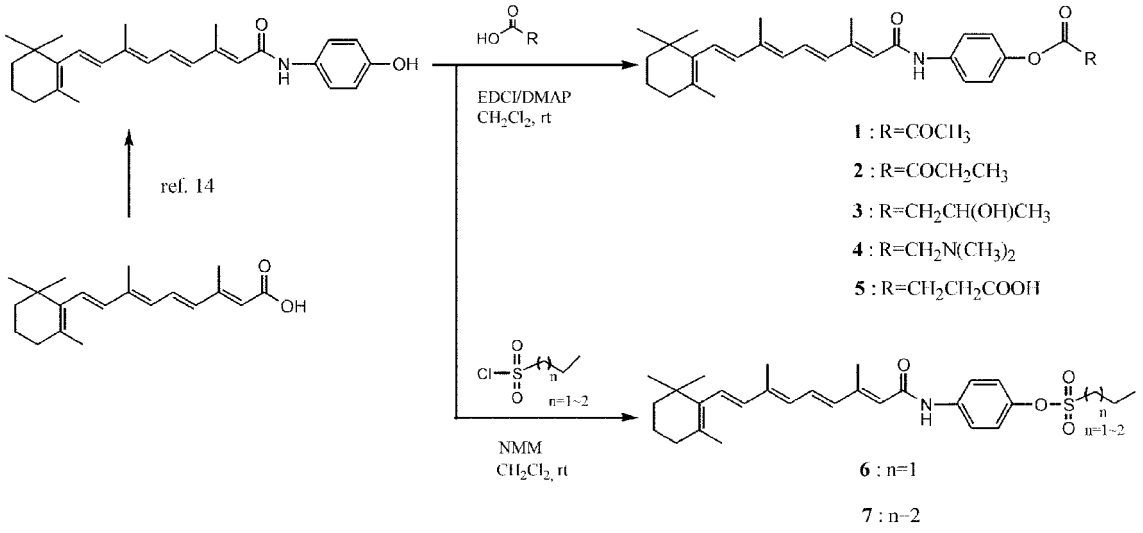
The synthesis of retinamide derivatives was carried out as follows. First, derivatives **1-5** were prepared by the coupling of various alkanoic acids and 4-HPR, under the conditions employing EDCI/DMAP at room temperature in dry DMF. α-Keto form **1** and **2** were obtained in low yields, due to decomposition upon purification. Second, derivatives **6** and **7** were synthesized from the reaction of 4-HPR and alkane sulfonyl chlorides in presence of *N*-methylmorpholine (NMM) in dry CH_2Cl_2.

As in Scheme 2, treating the requisite alkyl alcohol with stoichiometric amount of phosphorous oxychloride under Ar in anhydrous CH_2Cl_2 at reflux for 5 h provided the alkyl

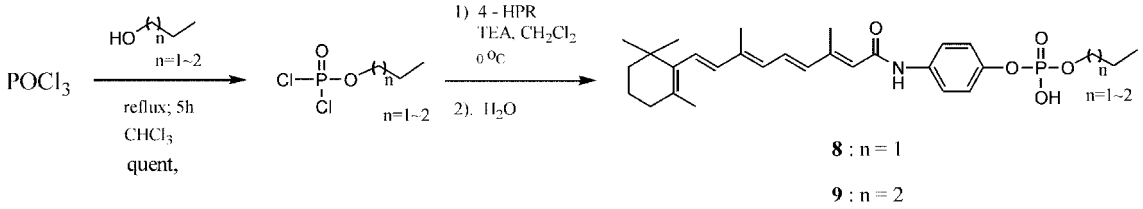


1 : R=$COCOCH_3$
2 : R=$COCOCH_2CH_3$
3 : R=$COCH_2CH(OH)CH_3$
4 : R=$COCH_2N(CH_3)_2$
5 : R= $COCH_2CH_2COOH$
6 : R= $SO_2CH_2CH_2CH_3$
7 : R= $SO_2CH_2CH_2CH_2CH_3$
8 : R= $PO_2(OH)CH_2CH_2CH_3$
9 : R= $PO_2(OH)CH_2CH_2CH_2CH_3$

Figure 2.



Scheme 1



Scheme 2

dichlorophosphate in a quantitative yield. Derivatives **8** and **9** were prepared by phosphorylation of 4-HPR with alkyl dichlorophosphates in the presence of triethylamine at 0 °C in dry CH_2Cl_2 and the hydrolysis of the corresponding adduct with H_2O in good yields.

Anti-proliferative effects of Retinamide derivatives. The growth suppressing potential of retinamide derivatives was investigated by determining their IC_{50} values (concentrations giving 50% growth inhibition) in HCT116 colon cancer cells. To determine the IC_{50} value, each derivative was treated at six different concentrations (0, 0.5, 1, 2.5, 5, 10 μM). As summarized in Table 1, IC_{50} of derivative **2** was 1.8 μM, four-fold better than 4-HPR (7.0 μM) in HCT116 cells. IC_{50} values of other derivatives were slightly better than (derivatives **3**, **4**, **5**, **7**), similar to (derivative **1**), or much worse than (derivatives **6**, **8**, **9**) that of 4-HPR. For better clinical outcome, we searched for retinoid derivatives with IC_{50} of submicromolar concentration and low side effects. Although the IC_{50} value of 4-HPR is relatively high, its relatively few side effects made it useful in clinical trial. In this regard, our derivative **2**, the most effective agent among the derivatives tested, could be a promising cancer drug, although its side effects remain to be determined by animal studies.

Table 1. IC_{50} values of retinamide derivatives in HCT116 colon cancer cells

Derivatives	IC_{50} (μM)
4-HPR	7.0
1	7.0
2	1.8
3	3.0
4	5.0
5	5.5
6	25.0
7	4.0
8	>100
9	>100

Experimental Section

Dry DMF was stored over 4 Å sieves and degassed before use by bubbling argon vigorously through for at least one hour. Dry CH_2Cl_2 was obtained from distillation over CaH_2. Commercially available reagents and solvents were used without further purification. All reactions were conducted under an Ar atmosphere, except for those reactions utilizing water as a solvent. They were monitored by TLC (Merck Kieselgel 60 F254). All the products prepared were purified by flash column chromatography using silica gel 60 (Merck, 230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-200F and JEOL JNM EX-400 using $CDCl_3$ as the solvent. All chemical shifts (δ) are quoted in ppm downfield from TMS and coupling constants (J) are given in Hz. Mass spectra were measured on a Shimazu GCMS-PO 1000 mass spectrometer (EI 70 eV).

General procedure I; A preparation of 4-HPR. A

mixture of dry DMF (0.077 mL, 0.99 mmol) and $SOCl_2$ (0.072 mL, 0.99 mmol) was stirred under argon for 1 h. To the solution was added all-trans retinoic acid (100 mg, 0.33 mmol) in dry DMF (2 mL). After being stirred at 0 °C for 45 mintues in subdued light, the clear deep red retinoyl chloride solution was added dropwise to a cooled solution of distilled triethylamine (0.14 mL, 0.99 mmol) and 4-aminophenol (0.072 g, 0.66 mmol) in dry, degassed DMF (2 mL). The temperature was maintained between 10-15 degrees during the addition. The dark colored reaction mixture was stirred at room temperature until TLC analysis indicated no remaining 4-aminophenol (about 2 h). The reaction was quenched with NH_4Cl (*aq.*) and extracted with EtOAc. The extracts were washed with H_2O and brine, dried (Na_2SO_4), and concentration. The residue was purified by column chromatography using a hexane/EtOAc (3/1) as the eluent to give HPR (0.118 mg, 91%) as a yellow solid.

General procedure II; 4-{[(2*E*,4*E*,6*E*,8*E*)-3, 7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenoyl]-amino}phenyl-2-oxobutanoate (1). To a solution of EDCI (97.7 mg, 0.510 mmol) in dry CH_2Cl_2 (10 mL) was added 2-ketobutyric acid (52.0 mg, 0.510 mmol) in dry CH_2Cl_2 (5 mL). The solution was stirred at room temperature for 0.5 h. To this mixture were added HPR (100 mg, 0.255 mmol) in dry DMF (2 mL) and DMAP (cat.) and the mixture was stirred for 2-3 h. The reaction was quenched with NH_4Cl (*aq.*), and the mixture was subjected to extraction with EtOAc (2 × 5 mL). The extracts were washed with H_2O and brine, dried (Na_2SO_4), and concentration. The residue was purified by column chromatography using hexane/EtOAc (3/1) as the eluent to give HPR-2-ketobutyrate (60 mg, 50%) as a yellow solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60 (d, 2H, J = 8.9 Hz), 7.13 (d, 2H, J = 8.9 Hz), 7.01 (dd, 1H, J = 14.8, 11.4 Hz), 6.09-6.32 (m, 4H), 5.78 (s, 1H), 2.98 (m, 2H), 2.42 (s, 3H), 2.01 (br s, 5H), 1.72 (s, 3H), 1.56-1.68 (m, 2H), 1.44-1.49 (m, 2H), 1.20 (t, 3H, J = 7.2 Hz), 1.03 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.14, 165.05, 159.32, 153.90, 151.30, 145.89, 139.55, 137.67, 137.21, 136.74, 136.66, 135.06, 130.75, 129.99, 129.43, 128.66, 125.45, 121.46, 120.58, 39.55, 34.24, 33.08, 33.02, 28.93, 21.74, 19.87, 13.72, 12.90, 11.17.

MS: *m/z* (%) = 69 (93), 109 (100), 119 (65), 161 (69), 202 (42), 255 (28), 391 (55), 475 (18, M^+).

4-{[(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenoyl]amino}phenyl-2-oxopropanoate(2). Yield: 52%

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60 (d, 2H, J = 8.9 Hz), 7.13 (d, 2H, J = 8.9 Hz), 7.01 (dd, 1H, J = 14.8, 11.4 Hz), 6.09-6.32 (m, 4H), 5.78 (s, 1H), 2.59 (s, 3H), 2.43 (s, 3H), 2.01 (br s, 5H), 1.72 (s, 3H), 1.56-1.68 (m, 2H), 1.44-1.49 (m, 2H), 1.03 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.03, 165.15, 151.30, 145.86, 139.56, 137.68, 137.21, 136.71, 135.98, 135.07, 130.76, 130.00, 129.43, 128.67, 121.39, 120.75, 120.62, 39.55, 34.24, 33.08, 29.68, 28.94, 26.82, 21.74, 19.18, 13.73, 12.91.

MS: *m/z* (%) = 69 (100), 109 (92), 149 (95), 201 (25), 255 (128), 391 (28), 461 (16, M^+).

4-{[(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenoyl]amino}phenyl-3-hydroxybutanoate (3). Yield: 62%

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.56 (d, 2H, J = 8.7 Hz), 7.25 (br s, 1H), 6.93-7.06 (m, 3H), 6.09-6.32 (m, 4H), 5.78 (s, 1H), 4.31-4.40 (m, 1H), 2.68-2.81 (m, 2H), 2.43 (s, 3H), 2.01 (br s, 5H), 1.72 (s, 3H), 1.56-1.68 (m, 2H), 1.44-1.49 (m, 3H), 1.20-1.38 (m, 2H), 1.03 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.20, 148.29, 138.39, 137.20, 136.80, 136.63, 135.27, 129.34, 129.17, 127.81, 121.86, 121.23, 121.08, 120.65, 120.58, 119.91, 63.67, 43.23, 33.76, 32.59, 28.50, 22.62, 22.56, 21.29, 19.18, 18.72, 13.15, 12.43.

MS: *m/z* (%) = 58 (100), 69 (77), 109 (77), 119 (64), 161 (56), 201 (33), 255 (32), 391 (23), 477 (28, M^+).

4-{[(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenoyl]amino}phenyl-2-(dimethylamino)acetate (4). Yield: 75%

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55 (d, 2H, J = 8.7 Hz), 7.05 (d, 2H, J = 8.7 Hz), 7.01 (dd, 1H, J = 14.8, 11.4 Hz), 6.09-6.31 (m, 4H), 5.78 (s, 1H), 2.44 (s, 6H), 2.42 (s, 3H), 2.01 (br s, 5H), 1.72 (s, 3H), 1.56-1.68 (m, 2H), 1.44-1.49 (m, 2H), 1.03 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.31, 150.78, 146.16, 139.29, 137.65, 137.23, 136.10, 135.22, 130.46, 130.13, 129.89, 129.47, 128.49, 122.14, 121.76, 121.09, 120.63, 115.74, 60.19, 45.20, 39.52, 34.20, 33.05, 29.65, 28.91, 21.73, 19.71, 13.66, 12.87.

MS: *m/z* (%) = 58 (100), 69 (6), 149 (8), 476 (73, M^+).

4-(4-{[(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenoyl]amino}phenoxy)-4-oxobutanoic acid (5). Yield: 72%

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40-7.50 (br s, 2H), 6.99-7.04 (m, 3H), 6.09-6.30 (m, 4H), 5.79 (s, 1H), 4.40-4.55 (br s, 1H), 2.82-2.84 (m, 4H), 2.40 (s, 3H), 2.00 (br s, 5H), 1.72 (s, 3H), 1.56-1.68 (m, 2H), 1.44-1.49 (m, 2H), 1.03 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.52, 171.23, 159.32, 146.16, 139.55, 137.71, 137.60, 137.19, 136.09, 135.57, 130.75, 130.00, 129.80, 129.53, 128.21, 122.11, 121.65, 120.36, 39.89, 34.14, 33.01, 29.32, 29.06, 28.97, 28.87, 21.67, 19.12, 13.55, 12.81.

MS: *m/z* (%) = 58 (100), 69 (22), 105 (9), 135 (8), 161 (8), 391 (7), 491 (35, M^+).

General procedure III; 4-{[(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenoyl]-amino}phenyl-1-propanesulfonate (6). To a cold solution of HPR (100 mg, 0.255 mmol) in dry CH_2Cl_2 (10 mL) and *N*-methylmorpholine (0.034 mL, 0.306 mmol) was added 1-propane sulfonyl chloride (0.034 mL, 0.306 mmol). After being stirred for 30 min, the mixture was further stirred for 2 h at room temperature. Saturated aqueous NH_4Cl was added into the mixture, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and concentration. The residue was purified by column chromatography (EtOAc/

Hexane = 1 : 3) to provide HPR-propyl sulfonate (95 mg, 75%) as a yellow solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.59 (d, 2H, J = 8.9 Hz), 7.18-7.27 (m, 3H), 7.01 (dd, 1H, J = 14.8, 11.4 Hz), 6.09-6.31 (m, 4H), 5.78 (s, 1H), 3.22 (d, 2H, J = 7.8 Hz), 2.41 (s, 3H), 1.95-2.06 (m, 7H), 1.72 (s, 3H), 1.56-1.68 (m, 2H), 1.44-1.49 (m, 2H), 1.10 (t, 3H, J = 7.3 Hz), 1.03 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.30, 151.24, 144.66, 139.52, 137.64, 137.41, 137.17, 135.07, 130.72, 129.97, 129.41, 128.64, 122.47, 120.90, 120.77, 51.87, 39.54, 34.21, 33.06, 28.91, 21.70, 19.16, 17.26, 13.72, 12.87, 12.80.

MS: *m/z* (%) = 108 (100), 123 (12), 215 (13), 497 (50, M^+).

4-{[(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenoyl]amino}phenyl-1-butanesulfonate (7). Yield: 73%

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.57 (d, 2H, J = 8.9 Hz), 7.53 (br s, 1H), 7.18 (d, 2H, J = 8.9 Hz), 7.01 (dd, 1H, J = 14.8, 11.4 Hz), 6.09-6.31 (m, 4H), 5.80 (s, 1H), 3.22 (d, 2H, J = 7.8 Hz), 2.41 (s, 3H), 1.87-2.01 (m, 7H), 1.72 (s, 3H), 1.56-1.68 (m, 2H), 1.44-1.49 (m, 4H), 1.01 (s, 6H), 0.97 (t, 3H, J = 7.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.23, 151.38, 144.71, 139.58, 137.66, 137.37, 137.19, 135.05, 130.80, 130.00, 129.41, 128.69, 122.52, 120.86, 120.70, 49.95, 39.54, 34.23, 33.07, 28.92, 25.36, 21.73, 21.39, 19.17, 13.73, 13.45, 12.89.

MS: *m/z* (%) = 108 (100), 136 (12), 204 (10), 511 (70, M^+).

General procedure IV; 4-{[(2*E*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenoyl]-amino}phenyl propyl hydrogen phosphate (8). To a solution propanol (0.8 mL, 0.010 mol) in dry CH_2Cl_2 (10 mL) was added $POCl_3$ (3.0 mL, 0.032 mol) dropwise at 0 °C. After being stirred at 0 °C for 1 h, the mixture was refluxed for 5 h, followed by vacuum distillation (bp 38-42 °C/0.2 torr) to afford propyl dichlorophosphate.

To a cooled solution of propyl dichlorophosphate (1 *eq.*) in dry CH_2Cl_2 (5 mL) were added HPR (0.1 g, 0.33 mmol) in dry CH_2Cl_2 (5 mL) and triethylamine (0.11 mL, 0.83 mmol). After being stirred for 1 h, H_2O (2 mL) was added into the mixture. The mixture was stirred for 2 h at room temperature and quenched with NH_4Cl (*aq.*). The aqueous layer was extracted with CH_2Cl_2 (2 ×), and the combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (EtOAc/Hexane = 1 : 2) to afford HPR-propyl phosphate (96 mg, 73%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, 2H, J = 7.8 Hz), 7.39 (br s, 1H), 7.15 (d, 2H, J = 8.7 Hz), 7.01 (dd, 1H, J = 14.8, 11.4 Hz), 6.12-6.30 (m, 4H), 5.79 (s, 1H), 4.28 (m, 2H), 2.41 (s, 3H), 2.02 (br s, 5H), 1.79-1.83 (m, 2H), 1.72 (s, 3H), 1.60-1.63 (m, 2H), 1.45-1.48 (m, 2H), 1.02 (s, 6H), 0.96-1.00 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.19, 151.73, 145.59, 139.51, 137.69, 137.22, 136.89, 135.13, 130.70, 129.99, 129.44, 128.65, 121.12, 120.85, 120.80, 72.15, 72.08, 39.58, 34.24, 33.09, 28.94, 23.29, 21.74, 19.20, 13.72, 12.91.

MS: *m/z* (%) = 108 (100), 119 (41), 159 (71), 202 (25), 225 (18), 391 (38), 513 (66, M^+).

Butyl-(4-{[(2,4,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenoyl]amino}phenyl) hydrogen phosphate (9). Yield: 71%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (br s, 1H), 7.55 (d, 2H, J = 7.8 Hz), 7.15 (d, 2H, J = 8.7 Hz), 6.99 (dd, 1H, J = 14.8, 11.4 Hz), 6.12-6.29 (m, 4H), 5.84 (s, 1H), 4.32 (m, 2H), 2.41 (s, 3H), 2.02 (br s, 5H), 1.74-1.81 (m, 2H), 1.72 (s, 3H), 1.60-1.63 (m, 2H), 1.41-1.48 (m, 4H), 1.03 (s, 6H), 0.97 (t, 3H, J = 7.3Hz),

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.29, 150.83, 144.89, 139.29, 137.66, 137.21, 136.69, 135.30, 130.43, 129.92, 129.48, 128.57, 120.99, 120.69, 120.64, 70.52, 70.44, 39.54, 34.22, 33.06, 31.74, 31.67, 28.91, 21.71, 19.17, 18.53, 13.67, 13.43, 12.87.

MS: *m/z* (%) = 69 (46), 108 (83), 119 (30), 201 (20), 255 (15), 391 (14), 527 (42, M^+).

Cell proliferation assays. Effects of 4-HPR derivatives on the proliferation of cervical cancer cell were determined using MTT assay kit (Sigma Co., St. Louis, MO) according to the manufacturers manual. Cells were grown in 96 well-microtiter plates starting at an initial density of 3×10^3 cells/100 mL medium/well. After 12 h from seeding, indicated concentrations of derivatives were added to the medium, and the cells were further grown for 48 h. The use of 0.01% DMSO as control of RA, did not affect proliferation of cells tested. After 4 h incubation with MTT reagent, the media was removed. DMSO (150 mL) was added to precipitate and the absorbance at 550 nm was measured using Spectra MAX 250 microplate spectrophotometer (Molecular Devices, Sunnyvale, CA). The results were expressed as mean values of the absorbances of at least four wells.

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