Supplementary Information belonging to the paper

Investigations in dendrimer space reveal solid and liquid tumor growth-inhibition by original phosphorus-based dendrimers and corresponding monomers and dendrons with ethacrynic acid motifs

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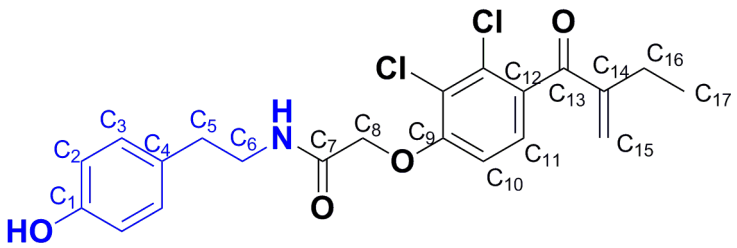
Monomeric and dendritic ethacrynic acid derivatives

The syntheses were carried out using standard high vacuum and dry-argon techniques. All chemicals were purchased from Acros, Aldrich, Fluka, and used without further purification. The solvents were freshly dried and distilled according to standard procedures prior to use.

^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded with Bruker AV300, DPX300, AV400, spectrometers. All ^{13}C NMR and ^{31}P NMR spectra were generally recorded decoupled {^{1}H}. Fourier transformed infrared (FTIR) spectra were obtained with a Perkin–Elmer Spectrum 100 FT-IR spectrometer on neat samples (ATR FT-IR) or in solutions. Mass spectrometry was carried out with a Thermo Fisher DS QII (DCI/NH_3 or DCI/CH_4).

Synthesis of 13

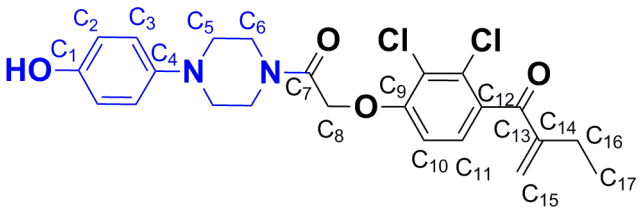


13

Procedure: To a mixture of tyramine (136 mg, 1 mmol) and ethacrynic acid (300 mg, 1 mmol) in dry DMF (8 mL) were added at room temperature EDCI (230 mg, 1.2 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred overnight at room temperature. Ethyl acetate (150 mL) was added and the organic layer was washed with water (2 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The crude product was purified by flash chromatography (DCM/EtOAc 90:10 to 80:20) to give the desired compound **13** as a white powder.

Yield = 60%. ^{1}H NMR ($CDCl_3$; 300 MHz), δ (ppm): 1.17 (t, $^3J_{HH}$ = 7.4 Hz, 3H, $C_{17}H_3$), 2.49 (q, $^3J_{HH}$ = 7.4 Hz, 2H, $C_{16}H$), 2.81 (t, $^3J_{HH}$ = 6.6 Hz, 2H, C_5H), 3.65 (q, $^3J_{HH}$ = 6.6 Hz, 2H, C_6H), 4.56 (s, 2H, C_8H), 5.61 (s, 1H, $C_{15}H$), 6.00 (s, 1H, $C_{15}H$), 6.64 (s, 1H, NH), 6.83 (d, $^3J_{HH}$ = 8.6 Hz, 1H, $C_{10}H$), 6.87 (d, $^3J_{HH}$ = 8.7 Hz, 2H, C_2H), 7.13 (d, $^3J_{HH}$ = 8.7 Hz, 2H, C_3H), 7.18 (d, $^3J_{HH}$ = 8.6 Hz, 1H, $C_{11}H$). **^{13}C {^{1}H} NMR ($CDCl_3$; 75 MHz), δ (ppm)**: 12.4 (s, C_{17}), 23.4 (s, C_{16}), 34.7 (s, C_5), 40.2 (s, C_6), 68.0 (s, C_8), 110.4 (s, C_2), 115.8 (s, C_{10}), 122.8 (s, C_{12}),127.1 (s, C_{11}), 128.7 (s, C_{15}), 129.5 (s, C_4), 129.6 (s, C_3), 131.4 (s, C_{11}'), 133.9 (s, C_{10}'), 150.2 (s, C_{14}), 154.4 (s, C_1), 154.8 (s, C_9), 166.9 (s, C_7), 196.2 (s, C_{13}).**HRMS (+ESI)** *m/z*: $[M+H]^+$ = 422.0929 ; **IR (neat):** ν= 3404 (NH), 3316 (OH), 1661 (C=O) cm^{-1}

Synthesis of 14



14

Procedure: To a mixture of phenolpiperazine (190 mg, 1.07 mmol) and ethacrynic acid (307 mg, 1.01 mmol) in dry DMF (6 mL) were added at room temperature EDCI (230 mg, 1.2 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred overnight at room temperature. Ethyl acetate (150 mL) was added and the organic layer was washed with water (2 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The crude product was purified by flash chromatography (DCM/EtOAc 90:10 to 80:20) to give **14** as a yellow powder.

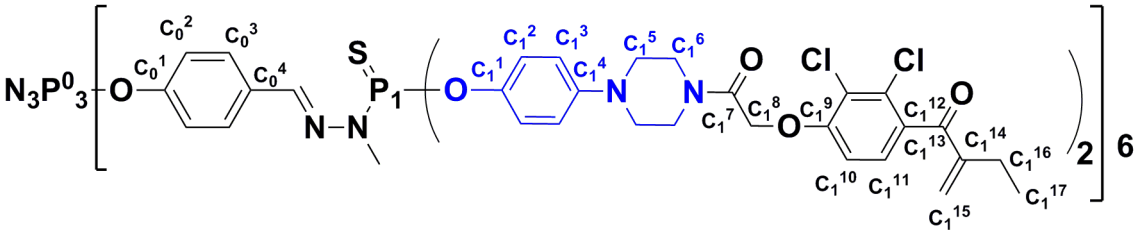
Yield = 60 %. ^{1}H NMR ($CDCl_3$; 400 MHz), δ (ppm): 1.16 (t, $^3J_{HH}$ = 7.4 Hz, 3H, $C_{17}H_3$), 2.48 (q, $^3J_{HH}$ = 7.4 Hz, 2H, $C_{16}H$), 2.99-3.06 (m, 2H, C_5H), 3.06-3.12 (m, 2H, C'_5H), 3.76-3.84 (m, 4H, C_6H and C'_6H), 4.88

(s, 2H, C_8H), 5.54 (s, 1H, OH), 5.61 (s, 1H, $C_{15}H$), 5.95 (s, 1H, $C_{15}H$), 6.79 (d, $^3J_{HH}$ = 9.0 Hz, 2H, C_2H), 6.84 (d, $^3J_{HH}$ = 9.0 Hz, 2H, C_3H), 7.00 (d, $^3J_{HH}$ = 8.6 Hz, 1H, $C_{10}H$), 7.16 (d, $^3J_{HH}$ = 8.6 Hz, 1H, $C_{11}H$). **^{13}C {^{1}H} NMR ($CDCl_3$; 101 MHz), δ (ppm)**: 12.4 (s, C_{17}), 23.4 (s, C_{16}), 42.4 (s, C_6), 45.7 (s, C'_6), 50.9 (s, C_5), 51.5 (s, C'_5), 68.7 (s, C_8), 110.37 (s, C_{10}), 116.0 (s, C_2), 119.3 (s, C_3), 122.8 (s, C'_{10}), 127.1 (s, C_{11}), 128.8 (s, C_{15}), 131.4 (s, C'_{11}), 133.8 (s, C_{12}), 144.9 (s, C_1), 150.2 (s, C_{14}), 150.7 (s, C_4), 155.2 (s, C_9), 165.3 (s, C_7), 195.8 (s, C_{13}).**HRMS (+ESI)** *m/z*: $[M+H]^+$ = 463.1188 ; **IR (neat):** ν = 3325 (OH), 1654 (C=O), 1645 (C=C) cm^{-1}

Synthesis of 15, 16 and 17.

General procedure

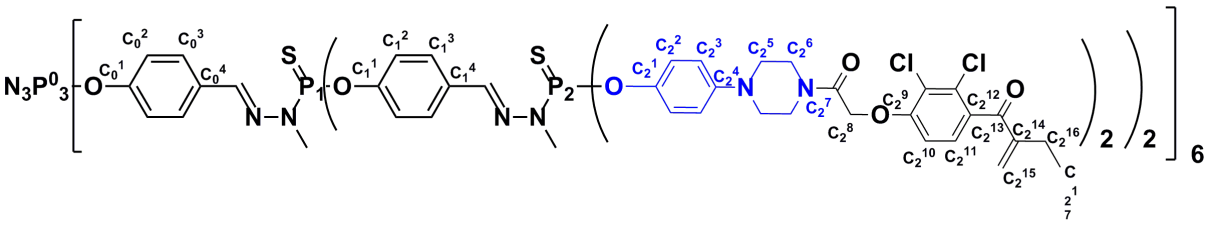
A dendrimer **Gn** (100 mg, 0.055 mmol, n=1), (100 mg, 0.021 mmol, n=2) or (100 mg, 0.01 mmol, n=3), was dissolved in THF (20 ml), and then appropriate masses of phenol **14** (321 mg, 0.693 mmol, n=1), (245 mg, 0.53 mmol, n=2) or (218 mg, 0.47 mmol, n=3), and cesium carbonate (430 mg, 1.32 mmol, n=1), (328 mg, 1.01mmol, n=2), (312 mg, 0.96 mmol, n=3), were added. The reaction mixture was stirred overnight at room temperature, and then centrifuged. The solution was concentrated and precipitated two times in pentane/ Et_2O (9/1). The product was filtered and dried under vacuum to give ***15*** (generation 1), ***16*** (generation 2) or ***17*** (generation3) as white powders.



15

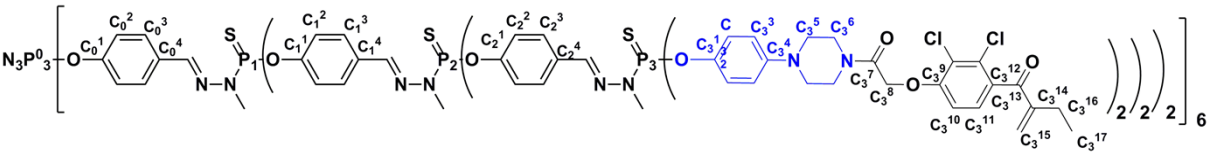
Yield = 86 %. ^{31}P {^{1}H} RMN (CD_2Cl_2 ; 162 MHz), δ (ppm): 8.59 (s, P_0), 64.22 (s, P_1). **^{1}H NMR (CD_2Cl_2 ; 400 MHz), δ (ppm)**: 1.15 (t, $^3J_{HH}$ = 7.4 Hz, 36H, $C_1{}^{17}H_3$), 2.46 (q, $^3J_{HH}$= 7.4 Hz, 24 H, $C_1{}^{16}H_2$), 3.06 (s, 24H, $C_1{}^5H_2$), 3.12 (s, 24H, $C'_1{}^5$), 3.27 (d, $^3J_{HP}$ = 10.0 Hz, 18H, CH_3N-P_1), 3.55-3.78 (m, 48H, $C_1{}^6$ and $C'_1{}^6$), 4.86 (s, 24H, $C_1{}^8H_2$), 5.60 (s, 12H, $C_1{}^{15}H_2$), 5.96 (s, 12H, $C_1{}^{15}H_2$), 6.81 (d, $^3J_{HH}$= 7.9 Hz, 24H, $C_1{}^3H$), 6.96 (d, $^3J_{HH}$ = 8.6 Hz, 12H, $C_1{}^{10}H$), 7.01 (d, $^3J_{HH}$ = 8.5 Hz, 12H, $C_0{}^2H_2$), 7.09 (d, $^3J_{HH}$ = 7.9Hz, 24H, $C_1{}^2H$), 7.18 (d, $^3J_{HH}$ = 8.6 Hz, 12H, $C_1{}^{11}H$), 7.62-7.71 (m, 18H, $C_0{}^3H$, C_0H=N).**^{13}C {^{1}H} NMR (CD_2Cl_2; 101 MHz), δ (ppm)**: 12.21 (s, $C_1{}^{17}$), 23.4 (s, $C_1{}^{16}$), 33.02 (d, $^2J_{CP}$ = 11.5 H, CH_3N-P_1), 41.83 (s, $C_1{}^6$), 45.05 (s, $C'_1{}^6$), 49.29 (s, $C_1{}^5$), 49.85 (s, $C'_1{}^5$), 68.22 (s, $C_1{}^8$), 110.87 (s, $C_1{}^{10}$), 117.33 (s, $C_1{}^3$), 121.33 (s, $C_0{}^2$), 121.90 (d, $^3J_{CP}$ = 4.1 Hz,

C_1^2), 122.51 (s, C_1^{12}), 127.06 (s, C_1^{11}), 128.22 (s, C_0^3), 128.54 (s, C_1^{15}), 131.00 (s, C_1^9), 132.49 (s, C_0^4), 133.52 (s, $C_1'^{10}$), 138.46 (d, $^3J_{CP}$ =14.5, C_0H=N), 143.98 (d, $^2J_{CP}$ = 7.2 Hz, C_1^1), 148.56 (s, C_1^4), 150.14 (s, C_1^{14}), 151.13 (s, C_0^1) 155.41 (s, $C_1'^{11}$), 164.79 (s, C_1^7), 195.48 (s, C_1^{13}).



16

Yield = 83 %. ^{31}P {^{1}H} RMN (CD_2Cl_2 ; 121 MHz), δ (ppm): 8.44 (s, P_0), 62.48 (s, P_1), 64.40 (s, P_2). **^{1}H NMR (CD_2Cl_2 ; 400 MHz), δ (ppm)**: 1.14 (t, $^3J_{HH}$ = 7.4 Hz, 72H, $C_2^{17}H_3$), 2.44 (q, $^3J_{HH}$= 7.3 Hz, 48H, $C_2^{16}H_2$), 3.06 (s, 48H, $C_2^5H_2$), 3.12 (s, 48H, $C'_2{}^5$), 3.17-3.31 (m, 54H, CH_3N-$P_{1,2}$), 3.55-3.78 (m, 96H, C_2^6 and $C'_2{}^6$), 4.84 (s, 48H, $C_2^8H_2$), 5.58 (s, 24H, $C_2^{15}H_2$), 5.96 (s, 24H, $C_2^{15}H_2$), 6.79 (d, $^3J_{HH}$ = 7.9 Hz, 48H, C_2^3H), 6.90-6.99 (m, 36H, C_2^{10}H and $C_0^2H_2$), 7.06 (d, $^3J_{HH}$ = 7.9Hz, 24H, C_2^2-H), 7.15 (d, $^3J_{HH}$ = 8.5 Hz, 12H, C_2^{11}H), 7.20 (d, $^3J_{HH}$ = 7.6 Hz, 24H , C_1^2H), 7.55-7.72 (m, 54H, C_0^3-H, C_1^3-H, C_0H=N and C_1H=N). **^{13}C {^{1}H} NMR (CD_2Cl_2; 101 MHz), δ (ppm)**: 12.23 (s, C_2^{17}), 23.39 (s, C_2^{16}), 32.72-33.12 (m, CH_3N-$P_{1,2}$), 41.82 (s, C_2^6), 45.02 (s, $C'_2{}^6$), 49.25 (s, C_2^5), 49.78 (s, $C'_2{}^5$), 68.14 (s, C_2^8), 110.88 (s, C_2^{10}), 117.29 (s, C_2^3), 121.24 (d, $^3J_{CP}$ = 2.3 Hz, C_0^2), 121.74 (d, $^3J_{CP}$ = 4.0 Hz, C_1^2), 121.94 (d, $^3J_{CP}$ = 3.9 Hz, C_2^2), 122.51 (s, C_2^{12}), 127.06 (s, C_2^{11}), 128.18 (s, C_1^3), 128.32 (s, C_0^3), 128.57 (s, C_2^{15}), 130.96 (s, C_2^9), 132.22 (s, C_0^4), 132.58 (s, C_1^4), 133.47 (s, $C_2'^{10}$), 138.61 (d, $^3J_{CP}$ = 12.9 Hz, C_1H=N), 139.35 (s, C_0H=N), 143.84 (d, $^2J_{CP}$ = 7.2 Hz, C_2^1), 148.55 (s, C_2^4), 150.11 (s, C_2^{14}), 151.15 (d, $^2J_{CP}$ = 7.0 Hz, C_0^1 and C_2^1), 155.41 (s, $C_2'^{11}$), 164.76 (s, C_2^7), 195.47 (s, C_2^{13}).



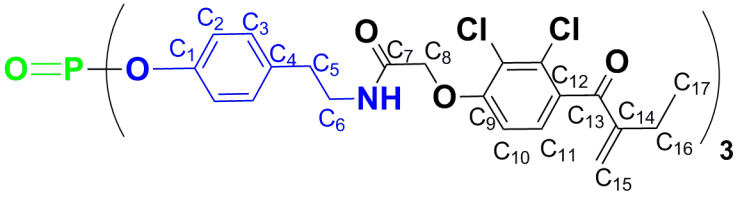
17

Yield = 81 %. ^{31}P {^{1}H} RMN (CD_2Cl_2 ; 121 MHz), δ (ppm): 7.95 (s, P_0), 62.58 (s, P_1), 64.26 (s, $P_{2,3}$). **^{1}H NMR (CD_2Cl_2 ; 400 MHz), δ (ppm)**: 1.11 (t, $^3J_{HH}$ = 7.4 Hz, 144H, $C_3^{17}H_3$), 2.42 (q, $^3J_{HH}$ = 7.3 Hz, 96H, $C_3^{16}H_2$), 3.02 (s, 96H, $C_3^5H_2$), 3.08 (s, 96H, $C'_2{}^5H_2$), 3.18-3.35 (m, 126H, CH_3N-$P_{1,2,3}$), 3.57-3.70 (m, 192H,

$C_2{}^6H_2$ and $C'_2{}^6H_2$), 4.82 (s, 96H, $C_3{}^8H_2$), 5.56 (s, 48H, $C_3{}^{15}H_2$), 5.93 (s, 48H, $C_3{}^{15}H_2$), 6.79 (d, $^3J_{HH}$ = 7.9 Hz, 96H, $C_3{}^3H$), 6.91 (d, $^3J_{HH}$ = 8.5 Hz, 60H, $C_3{}^{10}H_2$ and $C_0{}^2H_2$), 7.06 (d, $^3J_{HH}$ = 8.3Hz, 24H, $C_3{}^2H$), 7.13 (d, $^3J_{HH}$ = 8.5 Hz, 12H, $C_3{}^{11}H$), 7.21 (d, $^3J_{HH}$ = 7.6 Hz, 72H , $C_1{}^2H$ and $C_2{}^2H$), 7.58-7.83 (m, 126H, $C_0{}^3H$, $C_1{}^3H$, $C_2{}^3H$, C_0H=N, C_1H=N, C_2H=N and C_1H=N). **^{13}C {^{1}H} NMR (CD_2Cl_2; 101 MHz), δ (ppm)**: 12.24 (s, $C_3{}^{17}$), 23.40 (s, $C_3{}^{16}$), 32.67-33.17 (m, CH_3N-$P_{1,2,3}$), 41.82 (s, $C_3{}^6$), 44.99 (s, $C'_3{}^6$), 49.23 (s, $C_3{}^5$), 49.76 (s, $C'_3{}^5$), 68.09 (s, $C_3{}^8$), 110.89 (s, $C_3{}^{10}$), 117.28 (s, $C_3{}^3$), 121.20 (s, $C_0{}^2$), 121.77 (s, $C_1{}^2$ and $C_2{}^2$), 121.91 (d, $^3J_{CP}$ = 3.5 Hz, $C_2{}^3$), 122.45 (s, $C_3{}^{12}$), 127.06 (s, $C_3{}^{11}$), 128.18 (s, $C_2{}^3$), 128.35 (s, $C_1{}^3$), 128.47 (s, $C_0{}^3$), 128.60 (s, $C_3{}^{15}$), 130.93 (s, $C_3{}^9$), 132.22 (s, $C_0{}^4$), 132.58 (s, $C_1{}^4$ and $C_2{}^4$), 133.47 (s, $C_3{}'^{10}$), 138.70 (d, $^3J_{CP}$ = 12.5 Hz, C_2H=N), 139.21-139.76 (m, C_0H=N and C_1H=N), 143.88 (d, $^2J_{CP}$ = 7.3 Hz, $C_3{}^1$), 148.52 (s, $C_3{}^4$), 150.08 (s, $C_3{}^{14}$), 151.14-151.35 (m, $C_0{}^1$, $C_1{}^1$ and $C_2{}^1$), 155.42 (s, $C_3{}'^{11}$), 164.75 (s, $C_3{}^7$), 195.46 (s, $C_3{}^{13}$).

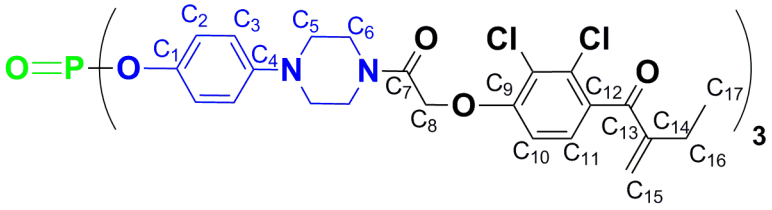
Synthesis of 18 and 19.

Procedure: To a solution of **13** (200 mg, 0.47 mmol) or **14** (205 mg, 0.47 mmol), in dry DCM (10 mL) were added triethylamine (109 µL, 79 mg, 0.78 mmol) and $POCl_3$ (12 µL, 20 mg, 0.14 mmol). The reaction mixture was stirred overnight at room temperature and concentrated under reduced pressure. The crude product was purified by flash chromatography (DCM/THF 90:10 to 80:20) to give ***18*** or ***19*** as white powders.



18

Yield = 35 %. ^{31}P {^{1}H} NMR ($CDCl_3$; 162 MHz), δ (ppm): -17.5 (s, P=O). **^{1}H NMR ($CDCl_3$; 400 MHz), δ (ppm)**: 1.13 (t, $^3J_{HH}$ = 7.4 Hz, 9H, $C_{17}H$), 2.45 (q, $^3J_{HH}$ = 7.4 Hz, 6H, $C_{16}H$), 2.86 (t, $^3J_{HH}$ = 6.6 Hz, 6H, C_5H), 3.63 (q, $^3J_{HH}$ = 6.6 Hz, 6H, C_6H), 4.53 (s, 6H, C_8H), 5.55 (s, 3H, $C_{15}H$), 5.93 (s, 3H, $C_{15}H$), 6.76-6.83 (m, 6H, NH and $C_{10}H$), 17.14 (d, $^3J_{HH}$ = 8.5 Hz, 3H, $C_{11}H$), 7.17-7.23 (s, 12H, C_2H, C_3H). **^{13}C {^{1}H} NMR ($CDCl_3$; 75 MHz), δ (ppm)**: 12.5 (s, C_{17}), 23.5 (s, C_{16}), 35.0 (s, C_5), 40.2 (s, C_6), 68.2 (s, C_8), 110.9 (s, C_{10}), 120.5 (d, $^3J_{CP}$ = 4.9 Hz, C_2), 123.0 (s, C_{12}), 127.3 (s, C_{11}), 128.9 (s, C_{15}), 130.3 (s, C_3), 131.5 (s, C_{11}'), 134.2 (s, C_{10}'), 135.9 (d, $^5J_{CP}$ = 1.0 Hz, C_4), 149.4 (d, $^2J_{CP}$ = 7.4 Hz, C_1), 150.3 (s, C_{14}), 154.5 (s, C_9), 166.8 (s, C_7), 195.6 (s, C_{13}). **HRMS (+ESI)** *m/z*: $[M+H]^+$ = 1311.2081; **IR (neat):** ν = 3417 (NH), 1664 (C=O) cm^{-1}

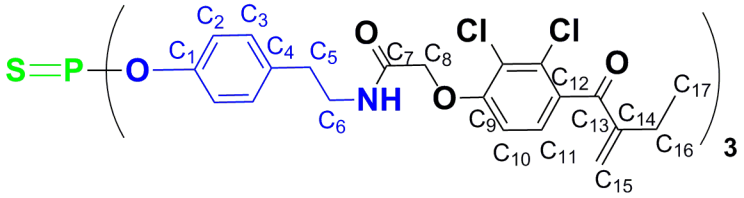


19

Yield = 85 %, ^{31}P {^{1}H} NMR ($CDCl_3$; 162 MHz) ; δ (ppm) : -16.1 (s, P=O). **^{1}H NMR ($CDCl_3$; 400 MHz), δ (ppm)**: 1.13 (t, $^{3}J_{HH}$ = 7.4 Hz, 9H, $C_{17}H_3$), 2.45 (q, $^{3}J_{HH}$ = 7.4 Hz, 6H, $C_{16}H$), 3.06-3.17 (m, 12H, C_5H and C'_5H), 3.73-3.81 (m, 12H, C_6H and C'_6H), 4.86 (s, 6H, C_8H), 5.58 (s, 3H, $C_{15}H$), 5.93 (s, 3H, $C_{15}H$), 6.83-6.86 (m, 6H, C_2H), 6.99 (d,$^{3}J_{HH}$ = 8.6 Hz, 3H, $C_{10}H$),7.10-7.18 (m, 9H, C_3H and $C_{11}H$). **^{13}C {^{1}H} NMR ($CDCl_3$; 101 MHz), δ (ppm)**: 12.5 (s, C_{17}), 23.6 (s, C_{16}), 42.2 (s, C_6), 45.6 (s, C'_6), 49.9 (s, C_5), 50.6 (s, C'_5), 68.9 (s, C_8), 110.8 (s, C_{10}), 118.1 (s, C_3), 121.0 (d, $^{3}J_{CP}$ = 4.7 Hz, C_2), 122.9 (s, C'_{10}), 127.2 (s, C_{11}), 128.8 (s, C_{15}), 131.6 (s, C'_{11}), 133.9 (s, C_{12}), 144.5 (d, $^{2}J_{CP}$ = 7.3 Hz, C_1), 148.6 (d, $^{5}J_{CP}$ = 1.0 Hz, C_4), 150.3 (s, C_{14}), 155.3(s, C_9), 165.3 (s, C_7), 195.9 (s, C_{13}). **HRMS (+ESI)** *m/z*: $[M+H]^+$ = 1435.2883; **IR (neat):** ν = 1663 (C=O) cm^{-1}

Synthesis of 20.

Procedure: To a solution of **13** (200 mg, 0.47 mmol), in dry DCM (10 mL) were added triethylamine (109 µL, 79 mg, 0.78 mmol) and $PSCl_3$ (15 µL, 25 mg, 0.15 mmol). The reaction mixture was stirred overnight at room temperature and concentrated under reduced pressure. The crude product was purified by flash chromatography (DCM/EtOAc 62:40) to give ***20*** as a white powder.



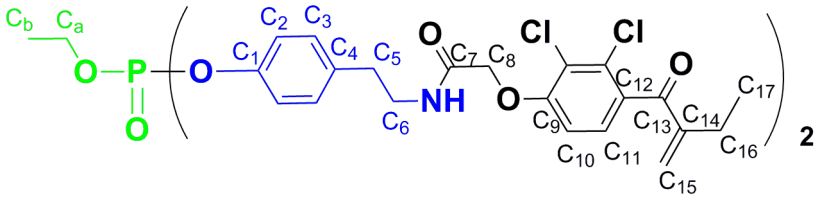
20

Yield = 35 %. ^{31}P {^{1}H} NMR ($CDCl_3$; 121 MHz), δ (ppm): 53.13 (s, P=S). **^{1}H NMR ($CDCl_3$; 300 MHz), δ (ppm)**: 1.16 (t, $^{3}J_{HH}$ = 7.4 Hz, 9H, $C_{17}H$), 2.48 (q, $^{3}J_{HH}$ = 7.4 Hz, 6H, $C_{16}H$), 2.89 (t, $^{3}J_{HH}$ = 6.9 Hz, 6H, C_5H), 3.68 (q, $^{3}J_{HH}$ = 6.9 Hz, 6H, C_6H), 4.56 (s, 6H, C_8H), 5.58 (s, 3H, $C_{15}H$), 5.96 (s, 3H, $C_{15}H$), 6.80 (s, NH) 6.83 (d, $^{3}J_{HH}$ = 8.5 Hz, 3H, $C_{10}H$), 17.16 (d, $^{3}J_{HH}$ = 8.5 Hz, 3H, $C_{11}H$), 7.23 (s, 12H, C_2H, C_3H). **^{13}C {^{1}H} NMR ($CDCl_3$; 75 MHz), δ (ppm)**: 12.4 (s, C_{17}), 23.4 (s, C_{16}), 34.9 (s, C_5), 40.0 (s, C_6), 68.1 (s, C_8), 110.8 (s, C_{10}),

121.4 (d, $^{3}J_{CP}$ = 4.8 Hz, C_2), 127.2 (s, C_{11}), 128.8 (s, C_{15}), 130.0 (s, C_3), 122.9 (s, C_{12}), 131.4 (s, C_{11}'), 134.1 (s, C_{10}'), 135.9 (d, $^{5}J_{CP}$ = 1.9 Hz, C_4), 149.4 (d, $^{2}J_{CP}$ = 8.0 Hz, C_1), 150.2 (s, C_{14}), 154.4 (s, C_9), 166.6 (s, C_7), 195.5 (s, C_{13}). **HRMS (+ESI)** *m/z*: $[M+H]^+$ = 1325.8998 ; **IR (neat):** ν = 3409 (NH), 1663 (C=O) cm^{-1}

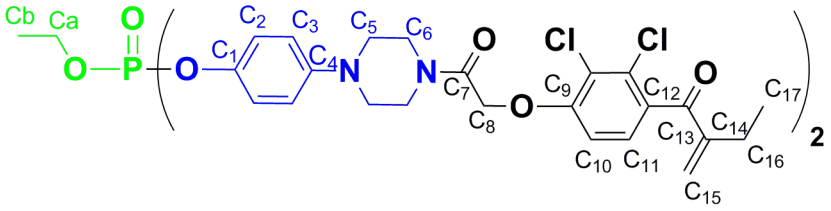
Synthesis of 21 and 22.

Procedure: To a solution of **13** (108 mg, 0.26 mmol) or **14 (**119 mg, 0.26 mmol) in dry DCM, (10 mL) were added triethylamine (68µL, 50 mg, 0.5 mmol) and dichloroethylphosphate (14 µL, 20 mg, 0.12 mmol). The reaction mixture was stirred overnight at room temperature and concentrated under reduced pressure. The crude product was purified by flash chromatography (DCM/THF 90:10 to 80:20) to give ***21*** or ***22*** as white powders.



21

Yield = 60%, $^{31}P\{^{1}H\}$ NMR (CDCl$_3$; 162 MHz) ; δ (ppm) : -11.76 (s, P=O). **^{1}H NMR (CDCl$_3$; 400 MHz); δ (ppm)** : 1.16 (t, $^{3}J_{HH}$ = 7.4 Hz, 6H, $C_{17}H_3$), 1.40 (t, $^{3}J_{HH}$ = 6.6 Hz, 3H, C_bH_3), 2.48 (q, $^{3}J_{HH}$ = 7.4 Hz, 4H, $C_{16}H$), 2.88 (t, $^{3}J_{HH}$ = 6.9 Hz, 4H, C_5H), 3.66 (q, $^{3}J_{HH}$ = 6.8 Hz, 4H, C_6H), 4.30-4.41 (m, 2H, C_aH_2), 4.55 (s, 4H, C_8H), 5.59 (s,1H, $C_{15}H$), 5.97 (s, 1H, $C_{15}H$), 6.80 (s, 1H, NH), 6.84 (d, $^{3}J_{HH}$ = 8.5 Hz, 4H, $C_{10}H$), 7.18 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H, $C_{11}H$), 7.21 (s, 8H, C_2H and C_3H). **$^{13}C\{^{1}H\}$ NMR (CDCl$_3$; 101 MHz), δ (ppm)** : 12.3 (s, C_{17}), 16.1 (d, $^{3}J_{CP}$ = 6.8 Hz, C_b), 23.4 (s, C_{16}), 34.8 (s, C_5), 40.0 (s, C_6), 65.5 (d, $^{2}J_{CP}$ = 6.1 Hz, C_a), 68.0 (s, C_8), 110.7 (s, C_{10}), 120.3 (d, $^{3}J_{CP}$ = 5.0 Hz, C_2), 122.8 (s, C_{12}), 127.1 (s, C_{11}), 128.7 (s, C_{15}), 130.0 (s, C_3), 131.4 (s, C'_{11}), 134.1 (s, C'_{10}), 135.3 (s, C_4), 149.40 (d, $^{2}J_{CP}$ = 7.1 Hz, C_1), 150.2 (s, C_{14}), 155.3 (s, C_9), 166.6 (s, C_7), 195.4 (s, C_{13}). **HRMS (+ESI)** *m/z*: $[M+H]^+$ = 935.1534 ; **IR (neat):** ν=3409 (NH), 1661 (C=O) cm^{-1}



22

Yield = 52 %, ^{31}P {^{1}H} NMR ($CDCl_3$; 162 MHz) ; δ (ppm) : -10.9 (s, P=O). **^{1}H NMR ($CDCl_3$; 400 MHz), δ (ppm)**: 1.14 (t, $^{3}J_{HH}$ = 7.4 Hz, 6H, $C_{17}H_3$), 1.35 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H, C_bH_3), 2.46 (q, $^{3}J_{HH}$ = 7.4 Hz, 4H, $C_{16}H$), 2.99-3.06 (m, 8H, C_5H and C'_5H), 3.73-3.81 (m, 8H, C_6H and C'_6H), 4.29 (q, $^{3}J_{HH}$ = 7.1 Hz, 2H, C_aH_2), 4.86 (s, 4H, C_8H), 5.58 (s, 2H, $C_{15}H$), 5.93 (s, 2H, $C_{15}H$), 6.86 (d, $^{3}J_{HH}$ = 8.6 Hz, 4H, C_2H), 6.99 (d,$^{3}J_{HH}$ = 8.6 Hz, 2H, $C_{10}H$),7.10-7.18 (m, 6H, C_3H and $C_{11}H$). **^{13}C {^{1}H} NMR ($CDCl_3$; 101 MHz), δ (ppm)**: 12.5 (s, C_{17}), 16.3 (d, $^{3}J_{CP}$ = 6.6 Hz, C_b), 23.6 (s, C_{16}), 42.3 (s, C_6), 45.6 (s, C'_6), 49.9 (s, C_5), 50.6 (s, C'_5), 65.5 (d, $^{2}J_{CP}$ = 6.3 Hz, *C*a), 68.9 (s, C_8), 110.8 (s, C_{10}), 118.2 (s, C_2), 119.3 (s, C_3), 122.9 (s, C'_{10}), 127.2 (s, C_{11}), 128.8 (s, C_{15}), 131.6 (s, C'_{11}), 133.9 (s, C_{12}), 144.6 (d, $^{2}J_{CP}$ = 7.3 Hz, C_1), 148.5 (d, $^{5}J_{CP}$ = 1.0 Hz, C_4), 150.3 (s, C_{14}), 155.3 (s, C_9), 165.3 (s, C_7), 195.9 (s, C_{13}). **HRMS (+ESI)** *m/z*: $[M+H]^+$ = 1017.2172 ; **IR (neat):** ν =1663 (C=O) cm^{-1}

Cell culture and proliferation assay. The human cell line KB (nasopharyngeal epidermis carcinoma) was originated from the NCI. Cells were grown in D-MEM medium supplemented with 10% fetal calf serum, in the presence of penicillin, streptomycin and fungizone in 75 cm^2 flask under 5% CO_2. HL60 (promyelocytic leukemia) and EPC (carp epithelium) cells from ATCC were grown in complete RPMI-1640 medium. Cells were plated in 96-well tissue culture with dendrimers dissolved in DMSO (1% final volume). After 72 h exposure, MTS reagent (Promega) was added and incubated for 3 h at 37°C: the absorbance was monitored at 490 nm and results are expressed as the inhibition of cell proliferation calculated as the ratio [(1-(OD490 treated/OD490 control))×100]. For IC_{50} determinations (50% inhibition of cell proliferation) experiments were performed in duplicate.