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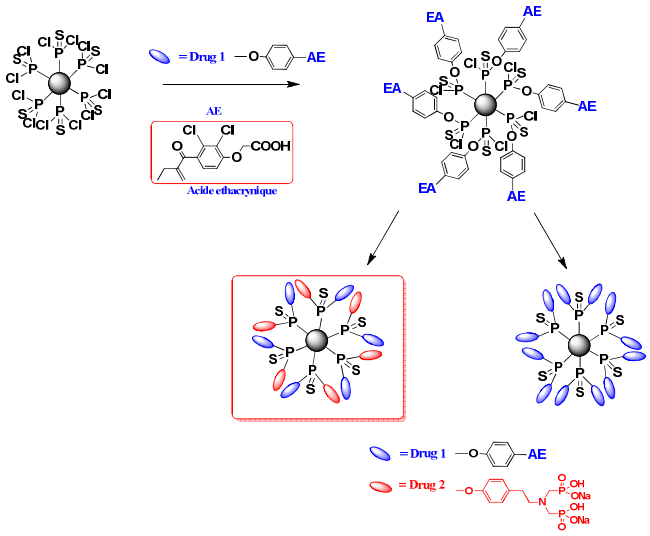
Graphical Abstract



Symmetrical and unsymmetrical incorporation of active biological monomers on the surface of phosphorus dendrimers

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Phosphorus-containing dendrimers are attractive carriers for the delivery of bioactive molecules due to their very particular architecture, globular shape and chemical and physical properties. Herein we report a simple synthetic approach of ethacrynic acid derivatives loaded-phosphorus dendrimers by symmetrical grafting of ethacrynic acid analogues by nucleophilic substitution of each chlorine of $P(S)Cl_2$ end groups. We report also for the first time an unsymmetrical grafting of two different phenol derivatives by a selective substitution of one chlorine of $P(S)Cl_2$ end group followed by the grafting of the second phenol.

Keywords: dendrimers, phosphorus, biological entities

Introduction

Dendrimers are a class of highly branched three dimensional macromolecules characterized by a well-defined nanostructure.[1] Dendrimers possess a large number of unique properties and constitute an increasingly important field of research in chemistry and in nanomedicine.[2] After pioneering works concerning dendrimers synthesis, the interest now is mainly focused on their applications.[3] Considerable effort has been devoted to the functionalization of dendrimers either on the periphery, between the branching units or at the core[4] to explore new properties and applications. Interestingly, the properties of these macromolecules are mainly depending on several factors as the nature of their functional end groups, the nature of their internal backbone and strongly, of their size.

The easiest way to achieve such multifunctional devices is the grafting in stochastic manner of several groups on the dendrimer surface.[5] This way was largely used for grafting a fluorophore[6] then a drug (e.g., 5-Fluorouracil (FU)[7], Doxorubicin (DOX)[8] or Methotrexate (MTX)[9]). For example, Baker et al.[10] have synthesized PAMAM dendrimer based multifunctional therapeutic devices containing MTX as an anticancer drug, fluorescein isothiocyanate (FITC) as an imaging agent and folic acid (FA) as a specific targeting agent. Unfortunately, the stochastic approach has a lot of limitations because the inconsistencies in the number of chemotherapeutic units loaded to dendrimers led often to unreproducible biological results.[11]

This concept has also been applied to phosphorus dendrimers (see their synthesis in Scheme 1) with the incorporation of diverse functional groups on their surface. For diverse applications, especially in biology, there is a need of dendrimers having several simultaneous functions (e.g. therapeutic, targeting, imaging) For example, ca. one FITC was grafted per first generation of phosphorus dendrimer covered by azabisphosphonate derivatives,[12] and a phosphorus dendrimer of generation 3 was prepared via a 10% stochastic labeling of the $P(S)Cl_2$ dendrimer terminal groups with a conjugate phenol julolidine followed by oligomannose substitution on

the remaining $P(S)Cl_2$ end groups.[13] In another interesting work, the specific unsymmetrical functionalization of phosphorus dendrimers bearing $P(X)Cl_2$ (X = O or S) end groups was carried out up to the generation 7 using different amine moieties to yield P(X)ClNRR' terminal functions. In a second step, either a second amine was reacted to afford P(X)NRR'NHR[1] terminal functions (up to generation 4) or a phenol to afford P(O)NRR'OAr terminal functions (up to generation 3).[14] To summarize, the symmetrical substitution of the chlorine group of $P(X)Cl_2$ units (X = O or S) could be attempted by amines,[15] phenolic entities,[16] organometallics,[16(b,e)] fluorophoric moieties[12,17] or sugar entities[18] to name as a few. Nevertheless, the sequential unsymmetrical substitution of the chlorines of the $P(S)Cl_2$ groups remains an exception.

In this paper, we report an approach for the simple control of the reactivity at the periphery of phosphorus-containing dendrimers allowing the sequential introduction of one or two different active molecules bearing a phenol group. For this purpose three phenol derivatives were selected: an azabisphosphonate **1**[19] the 4-hydroxybenzaldehyde, **EA-2**[20] (Figure 1) and modified ethacrynic acids (**EA-3** and **EA-4** see syntheses in Scheme 2).

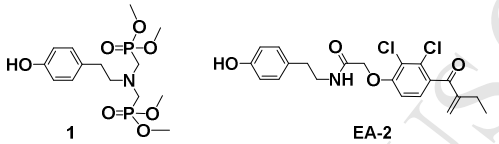


Fig. 1: Structure of the monomers **1** and **EA-2**

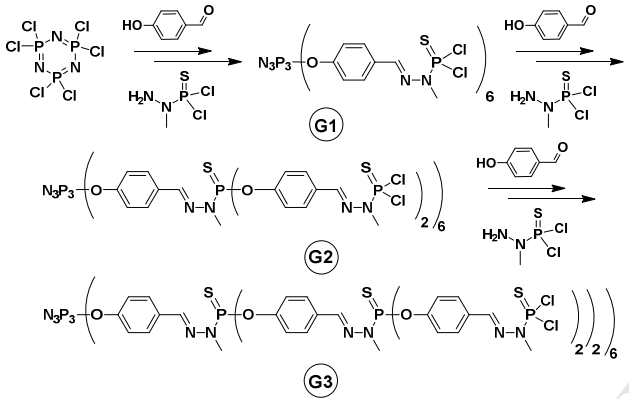
As far as we know, two different phenols have never been grafted selectively on the surface of dendrimers. The choice of these three different phenols was dictated by the following considerations.

- **i)** Ethacrynic acid or [2,3-dichloro-4-(2-methylene-1-oxobutyl)phenoxy] acetic acid belongs to the diuretic drugs,[21] has an acid function and a carbonyl unit α, β-unsaturated which is often used as inhibitor of glutathione-S-transferase P1-1 (GSTP1-1) overexpressed in a variety of cancer cells, especially, in chemotherapy-resistant cancer cells.[22] Very recently, we reported the grafting of ethacrynic acid analogues onto phosphorus dendrimer surface which afforded complexes with strong anti-proliferative activities against liquid and solid tumors.[20]
- **ii)** Beside the advances made in chemotherapy with the use of specific anticancer drugs, the increase of the immune system efficiency to fight against cancers is also another interesting challenge.[23] The artificial increase of the number of blood immune cells is very difficult recurring complex and poorly available biological entities. Interestingly, a phosphorus dendrimer of generation 1 prepared by nucleophilic substitution of its 6 terminal $P(S)Cl_2$ by aminobisphosphonate functionalized by a phenol displays a very interesting property, highly and selectively promoting the multiplication of human natural killer cells (NK).[19] Therefore it was of great interest to check if such an active phenol can be sequentially and unsymmetrically grafted to phosphorus dendrimers,
- **iii)** Grafting of a bifunctional reagent as 4-hydroxybenzaldehyde on residual P-Cl bonds offers the advantage to incorporate an additional function at the surface of the dendrimers (in this case aldehyde units) and therefore the possibility to diversify the properties of the resulting dendrimers.

Results and Discussion

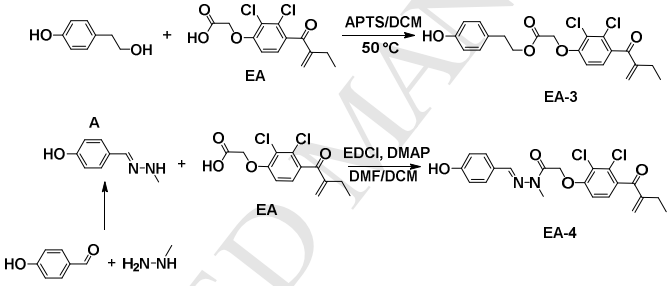
Phosphorus starting dendrimers were prepared as described in Scheme 1 using the reiteration of two steps, e.g., nucleophilic substitution and Schiff base reactions.[24] So, after the nucleophilic substitution of the six chlorine of the hexachlorocyclotriphosphazene $P_3N_3Cl_6$ [25]with 4-hydroxybenzaldehyde under basic conditions, the condensation reaction between the terminal aldehyde and $H_2NNMeP(S)Cl_2$ was carried out leading to generation 1 dendrimer (**G1**). This two-step route was repeated once or twice to achieve the formation of

dendrimers **G2** and **G3**, respectively. The synthesized dendrimers (**G1**, **G2** and **G3**) have $P(S)Cl_2$ as reactive end groups.



Scheme 1: Dendrimers generation **G1**-**G3** with **$P(S)Cl_2$** end groups

The grafting of several types of phenolic groups at each terminal $P(S)Cl_2$ unit could be attempted by simple substitution reaction. In continuation of our research concerning ethacrynic acid derivatives,[20] other phenolic ethacrynic acid derivatives were prepared (Scheme 2) and were later grafted on the surface of different generations of dendrimers **Gn** (**G1**, **G2** and **G3**).

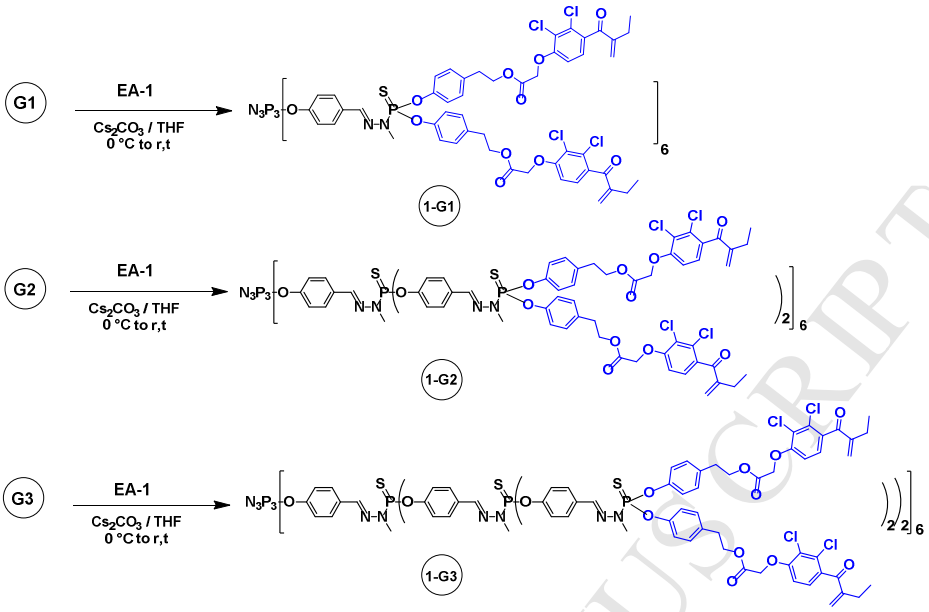


Scheme 2: Synthesis of **EA** derivatives **EA-3** and **EA-4** from **EA**

First, we started with the synthesis of **EA** derivatives **EA-3** and **EA-4** as shown in Scheme 2. Phenol **EA-3** was prepared in one step using the classical conditions of the esterification reaction, starting from the commercially available **EA** and 4-(2-hydroxyethyl)phenol in the presence of paratoluenesulfonic acid (APTS). The reaction mixture was heated at 50°C for 12h to provide **EA-3** in almost a quantitative yield (92%). For the preparation of **EA** amide (**EA-4**) a strategy based on two steps starting from 4-hydroxybenzaldehyde was used. The condensation of the 4-hydroxybenzaldehyde with methylhydrazine, led to (*E*)-4-((methylimino)methyl)phenol **A**, then a peptidic type reaction using **EA** in the presence of EDCI (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide) and a catalytic amount of DMAP (4-Dimethylaminopyridine) in DCM/DMF, afforded **EA-4** in 40 % yield.

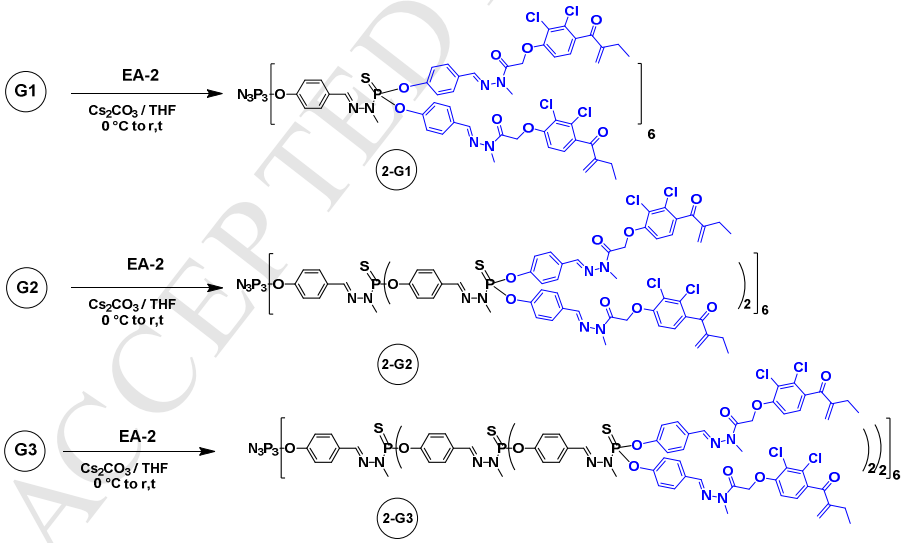
Then, we attempted the direct coupling of **EA-3** with **Gn** (n = 1, 2, 3) dendrimers. Using Cs_2CO_3 as base in THF**,** **EA** bearing a phenol group was successfully coupled to dendrimers bearing $P(S)Cl_2$ end groups. The reaction, carried out using different dendrimer's generations, led to **EA** decorated dendrimers **1-Gn** (n = 1-3, Scheme 3). The new dendrimers **1-G1**, **1-G2** and **1-G3** bear 12, 24 and 48 peripheral **EA** derivatives on their surface, respectively. These products were isolated in 90, 88 and 85% yield, respectively. Reactions were monitored by ^{31}P NMR spectroscopy which shows the disappearance of the signal due to the external **$P(S)Cl_2$** units at 63.1 ppm on behalf of a new signal at 62.9 ppm whatever the generation. It is noteworthy also that, in all **Gn,** the chemical shift corresponding to ^{31}P of $P(S)Cl_2$ end groups changes when the substitution of one chlorine occurred and changes again when two chlorine are substituted. In contrast, the chemical shift

corresponding to the dendrimer core **N_3P_3** did not change if a mono or a disubstitution occurred on the surface of the dendrimer.



Scheme 3: Grafting of the **EA-3** on the surface of **Gn** dendrimers

The same reaction was applied for the grafting of **EA-4** on the surface of different dendrimer generations **Gn** (n= 1-3). The resulting **EA**-decorated dendrimers **2-Gn** (n = 1-3, Scheme 4), bearing 12, 24 and 48 peripheral **EA** moieties, were obtained in 88, 85 and 85 % yield, respectively. Analogous modifications of the ^{31}P spectra than those observed for the **1-Gn** family were also observed.



Scheme 4: Grafting of the **EA-4** on the surface of **Gn** dendrimers

Then, we tried the direct coupling of **EA-2** onto **Gn**. We started by grafting **EA-2** on **G1** under the same reaction conditions as indicated above. The reaction, monitored by ^{31}P NMR spectroscopy, showed at the beginning two signals at 8.3 ppm (N_3P_3) and at 62.8 ppm (P=S groups) corresponding to the starting material **G1**. Then, the appearance of a signal at 68.3 ppm characteristic of the formation of the mono-substitution at the $P(S)Cl_2$ groups was detected. Subsequently, precipitation was observed in the reaction medium with the disappearance of all the NMR peaks, probably due to the formation of the di-substitution derivative. All the

attempts to solve this problem by varying the reaction solvent or changing the reaction temperature (from room temperature to 50°C) failed.

To explain this phenomenon, we thought about the possible formation of intra or inter hydrogen bonds, between the oxygen of the acrylate and the hydrogen of the amide function O-H…O=C, which can lead to the formation of aggregates due to di-substitution of **P(S)Cl$_2$**. This hypothesis seems to be supported by a X-ray study realized on phenol **AE-2** (Figure 2) which showed the formation of a hydrogen bond between the oxygen of the acrylate moiety and the hydrogen of the amide (distance between H(2)-O(8) = 2.811(10) Å).

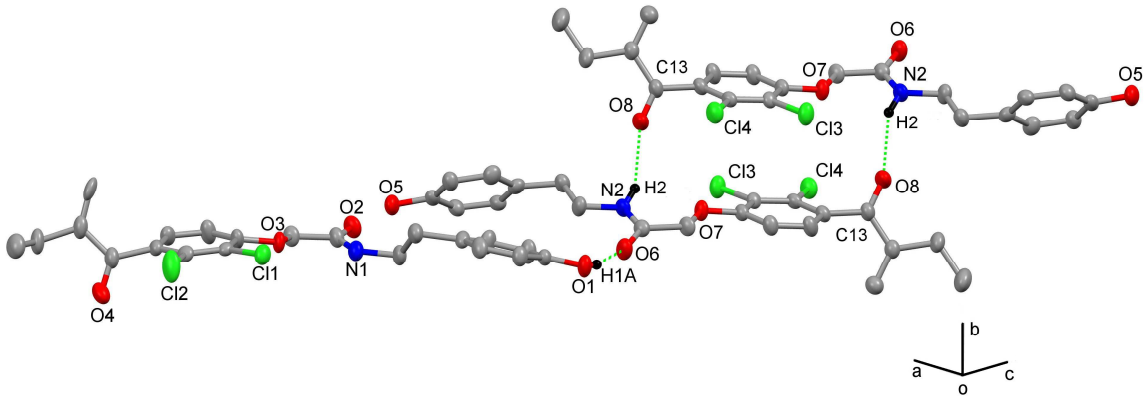


Fig. 2: X-ray structure of the monomer **AE-2**
Bond lengths N(2)-H(2)= 0.864(10) Å, C(13)-O(8)=1.230(04) Å and H(2)-O(8)=2.26(2) Å

It is very important to note that during this reaction, we observed the formation of the mono-substitution intermediate first then solubility problems occurred when the di-substitution started. Based on this interesting observation we decided to exploit this selectivity to introduce two different phenol moieties on dendrimer surface by an unsymmetrical di-substitution of the phosphorus end groups P(S)Cl$_2$.

The mono-substitution of P(S)Cl$_2$ end groups of **G1** was achieved using 6 equivalents of **EA-2** and 12 equivalents of Cs_2CO_3 in THF. The reaction was monitored particularly by ^{31}P NMR, which displays, in addition to the signal at 8.4 ppm corresponding to the chemical shift of the N_3P_3 core, a deshielding of the signal corresponding to the terminal groups on going from 63.1 ppm (P(S)Cl$_2$) to 68.3 ppm typical to the mono-substitution and a signal at 62.8 ppm corresponding to 5% of the di-substitution product (Figure 3).

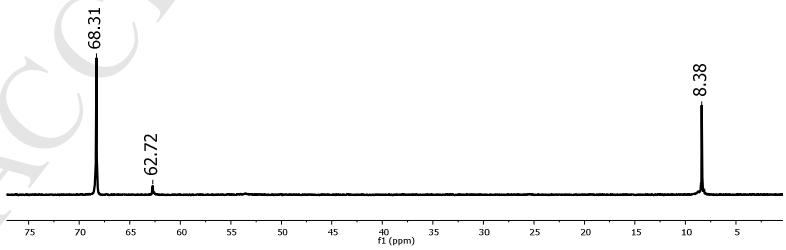
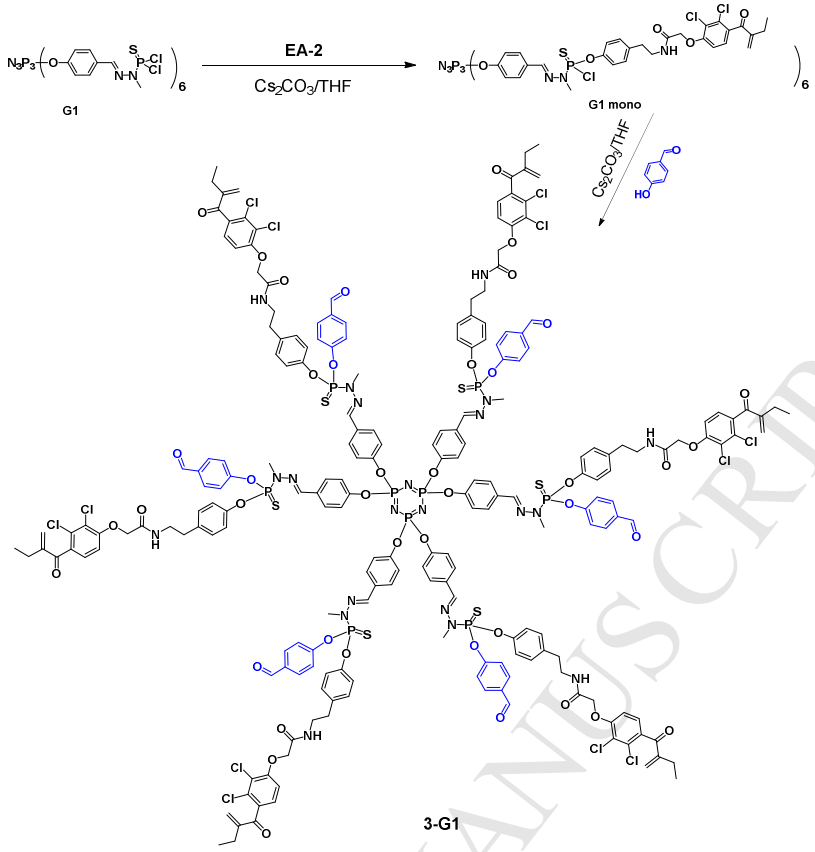


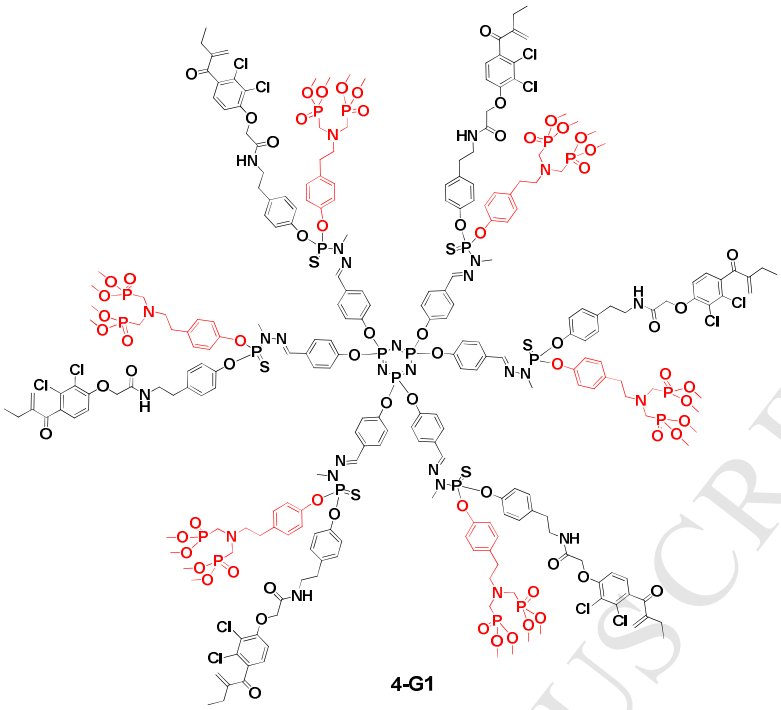
Fig. 3: ^{31}P NMR spectrum of mono-substitution dendrimer **G1mono**

This compound was obtained *in situ* and engaged in a second coupling reaction with other phenol derivatives. In the first example, the mono-substituted intermediate (**G1 mono**) was treated with 6 equivalents of 4-hydroxybenzaldehyde and 12 equivalents of Cs_2CO_3 in THF. The reaction mixture was stirred for 12h at room temperature and monitored by ^{31}P NMR; when the substitution of the second chlorine occurred, the chemical shift of N_3P_3 core was not modified while the P_1 (phosphorus of the first generation) shifted to 61.7 ppm (Figure 3). The desired product **3-G1** was obtained as a white powder in 72 % yield (Scheme 5).



Scheme 5: Grafting of the **EA-2** and 4-hydroxybenzaldehyde on the surface of **G1** dendrimers

In the second example, azabisphosphonate phenol **1** was grafted as a second active phenol onto the remaining Cl of the mono-substituted dendrimer (intermediate **G1 mono**) using 6 equivalents of **1** and 12 equivalents of Cs_2CO_3 in THF. The signal corresponding to the terminal groups moves from 68.3 ppm to 63.1 ppm with appearance of another signal at 26.5 ppm corresponding to the phosphonate groups of phenol **1** (Figure 4). The dendrimer **4-G1** was obtained as a white powder (65%) (Scheme 6). To our knowledge, two different phenols have never been grafted on such phosphorus dendrimers thus allowing to have on their surface two different bioactive molecules (NK multiplication, target 1 and caspase 3/7 activation (apoptotic enzymes),[26] target 2).



Scheme 6: Structure of **4-G1**

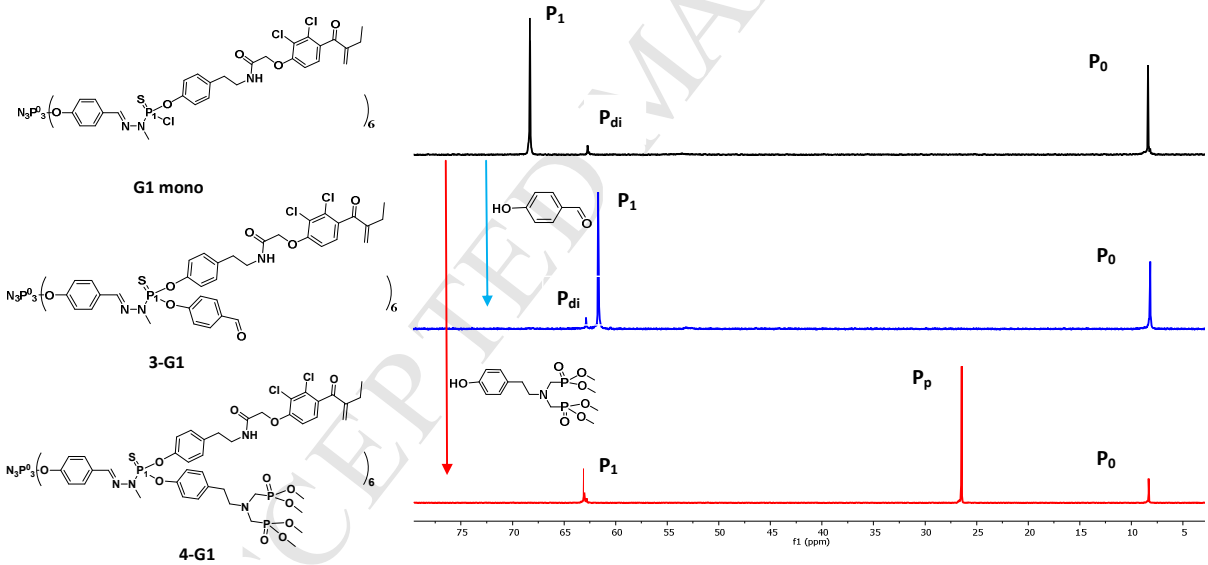


Fig. 4: ^{31}P NMR spectrum of **G1mono, 3-G1** and **4-G1**

Conclusions

In this study, we have developed a simple synthetic method allowing to graft phenol derivatives of drugs on the periphery of phosphorus dendrimers. We have also described the first phosphorus dendrimers containing two different phenol moieties in their periphery in a controlled fashion. This current approach will offer several opportunities for phosphorus containing dendrimers to diversify their surface by unsymmetrical substitution of the $P(S)Cl_2$ end groups. Taking into account the huge number of functionalized phenols that exist; this method opens thus an original and versatile way for the functionalization of dendrimer's surface.

Experimental Part

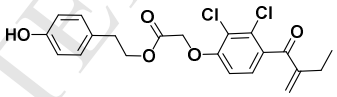
The syntheses were carried out using standard high vacuum and dry-argon techniques. All chemicals were purchased from Acros, Aldrich, Fluka, and used without further purification. The solvents were freshly dried and distilled according to standard procedures prior to use.

^{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}. The signal of the non-deuterated solvent served as internal standard, relative to $SiMe_4$ for ^{1}H and ^{13}C NMR, to H_3PO_4 for ^{31}P NMR. 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). The purity of phosphorhydrazone dendrimers cannot be assessed by mass spectrometry (ESI or MALDI-Tof) as both techniques induce dramatic cleavages of the structure.[27]

X-ray data were collected at low temperature (193(2) K) on a Bruker Kappa Apex II diffractometer equipped with a 30 W air-cooled microfocus, using MoKα radiation (λ = 0.71073 Å), and an Oxford Cryosystems Cryostream cooler device. Phi- and omega- scans were used for data collection. The structure was solved by direct methods with SHELXS-97.[28] All non-hydrogen atoms were refined anisotropically by means of least-squares procedures on F^2 with SHELXL-97.[Error! Bookmark not defined.] The hydrogen atoms were refined isotopically at calculated positions using a riding model except the N-bound H atoms which have been located in a difference Fourier map and refined with the N-H bond-length fixed at 0.88(1) Å. In the crystal structure, disorders were modeled successfully with the atom ellipsoids restrain by SIMU and DELU commands.The data of the crystal structure were deposited at the Cambridge crystallographic data centre and have been assigned to the following deposition numbers CCDC 1473464.

Compounds **1**[19] and **EA-2**[20] were prepared following the previously reported procedures.

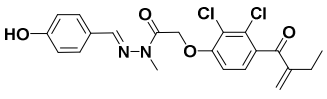
Synthesis of EA-3:



To a mixture of paratoluenesulfonic acid (APTS) (342 mg, 1.8 mmol) and ethacrynic acid (500 mg, 1.8 mmol) in DCM (10 mL), 4-(2-hydroxyethyl)phenol (250 mg, 1.8 mmol) was added at 0°C. The reaction mixture was heated to 50°C for 12h and then evaporated to dryness. The crude residue was purified by flash chromatography (hexane/EtOAc (6/4)) to furnish **EA-3.**

EA-3. White solid, 92% yield (0.642 g). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.18 (t, J =7.4 Hz, 3H), 2.49 (q, J = 7.4 Hz, 2H), 2.91 (t, J = 6.5 Hz, 2H), 4.40 (t, J = 6.5 Hz, 2H), 4.76 (s, 2H), 5.54 (s, 1H), 5.63 (s, 1H), 6.02 (s, 1H), 6.62 (d, J = 8.6 Hz, 1H), 6.69 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.6 Hz, 1H); ^{13}C {^{1}H} NMR (101 MHz, CD_2Cl_2) δ 12.2, 23.4, 33.9, 66.1, 66.2, 110.4, 115.3, 126.8, 129.2, 129.8, 122.7, 129.3, 131.1, 133.4, 150.2, 154.5, 155.4, 167.7, 196.3. HRMS (+ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{20}Cl_2O_5$: 423.0766, found, 423.0773. Anal. Calcd for $C_{21}H_{20}Cl_2O_5$: C, 59.59; H, 4.76; found: C, 59.49; H, 4.70. IR (neat): ν = 3316 (OH), 1661 (C=O) cm^{-1}

***Synthesis of EA-4*:**



To a solution of *p*ara-hydroxybenzaldehyde (1.65 g, 13.5 mmol) in dry THF (40 mL), monomethylhydrazine (0.71 mL, 621 mg, 13.5 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature and monitored by TLC. The reaction mixture was concentrated under reduced pressure to give the expected 4-((2-methylhydrazono)methyl)phenol as a yellow oil.

To a solution of crude 4-((2-methylhydrazono)methyl)phenol (1.0 g, 6.66 mmol) in a DCM/DMF mixture (60 mL, 2:1), ethacrynic acid (2.10 g, 6.93 mmol), EDCI (1.50 g, 7.82 mmol) and a catalytic amount of DMAP were added. The reaction mixture was stirred for 40 h at room temperature. Ethyl acetate (300 mL) was added and the organic layer was washed with water (2 × 100 mL) and brine (4 × 100 mL), dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The crude product was purified by flash chromatography (DCM/EtOAc 98:2 to 95:5) to give the **EA-4** as a yellow powder.

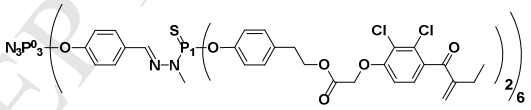
EA-4. Yellow solid, 40% yield (1.2 g). ^{1}H NMR (400 MHz, d_8-THF) δ 1.16 (t, J =7.4 Hz, 3H), 2.47 (q, J = 7.4 Hz, 2H), 3.38 (s, 3H), 5.48 (s, 2H), 5.61 (s, 1H), 5.95 (s, 2H), 6.82 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 8.6 Hz, 2H), 7.87 (s, 1H), 8.68 (s, 1H); ^{13}C {^{1}H} NMR (101 MHz, d_8-THF) δ 11.9, 23.4, 26.7, 67.2, 111.1, 115.4, 122.2, 126.2, 126.6, 126.9, 128.5, 130.3, 132.8, 140.1, 150.4, 156.7, 159.5, 166.9, 194.5. HRMS (+ESI) *m/z*: $[M+H]^+$ = 435.0870. Anal. Calcd for $C_{21}H_{20}Cl_2N_2O_4$: C, 57.94; H, 4.64; N,6.44; found C, 57.89; H, 4.58; N, 6.40. IR (neat): ν = 3475 (OH), 1688 (C=O), 1649 (C=N) cm^{-1}

Synthesis of 1-Gn:

General procedure

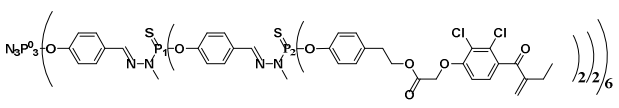
A dendrimer **Gn** (100 mg, 0.055 mmol, n = 1), (100 mg, 0.021 mmol, n = 2) or (100 mg, 0.01 mmol, n = 3), was dissolved in THF (20 mL), and then the appropriate masses of phenol **EA-3** (291 mg, 0.687 mmol, n = 1), (222 mg, 0.525 mmol, n = 2) or (201 mg, 0.48 mmol, n = 3), and cesium carbonate (430 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 to remove salts. The solution was concentrated and precipitated two times in pentane/Et_2O (9/1). The product was filtered and dried under vacuum to give **1-G1** (generation 1), **1-G2** (generation 2) or **1-G3** (generation 3) as white powders.

***Synthesis of* 1-G1:**



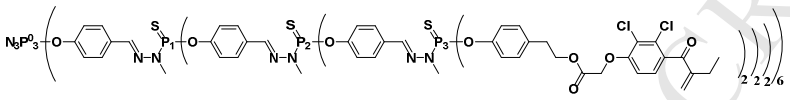
White solid, 90% yield (0.393 g). ^{31}P {^{1}H} NMR (121 MHz, CD_2Cl_2) δ 8.32 (s, P_0), 62.90 (s, P_1). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.14 (t, J = 7.4 Hz, 36H), 2.45 (q, J = 7.4 Hz, 24 H), 2.91 (t, J = 6.8 Hz, 24H), 3.28 (d, J = 10.2 Hz, 18H), 4.37 (t, J = 6.8 Hz, 24H), 4.71 (s, 24H), 5.58 (s, 12H), 5.95 (s, 12H), 6.74 (d, J = 8.6 Hz, 12H), 7.03 (d, J = 8.6 Hz, 12H), 7.08-7.22 (m, 60H), 7.60-7.68 (m, 18H); ^{13}C {^{1}H} NMR (75 MHz, CD_2Cl_2) δ 12.2, 23.4, 32.9 (d, J = 12.0 Hz), 34.1, 65.6, 66.1, 110.7, 121.2, 121.3 (d, J = 4.7 Hz), 122.8, 126.9, 128.2, 128.6, 130.0, 131.1, 132.3, 133.7, 134.8 (d, J = 1.7 Hz), 138.5 (d, J = 13.5 Hz), 149.4 (d, J = 7.1 Hz), 150.1, 151.2, 155.3, 167.5, 195.4. Anal. Calcd for $C_{300}H_{276}N_{15}Cl_{24}O_{66}P_9S_6$: C, 55.70; H, 4.30; N, 3.25; found: C, 55.59; H, 4.19; N, 3.14.

***Synthesis of* 1-G2:**



White solid, 88% yield (0.334 g). ^{31}P {^{1}H} NMR (121 MHz, CD_2Cl_2) δ 8.3 (s, P_0), 62.6 (s, P_1), 62.9 (s, P_2); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.12 (t, *J* = 7.4 Hz, 72H), 2.43 (q, *J* = 7.4 Hz, 48H), 2.90 (t, *J* = 6.8 Hz, 48H), 3.29 (m, 56H), 4.36 (t, *J* = 6.8 Hz, 48H), 4.70 (s, 48H), 5.56 (s, 24H), 5.94 (s, 24H), 6.72 (d, *J* = 8.5 Hz, 24H), 7.00 (d, *J* = 7.8 Hz, 12H), 7.08-7.28 (m, 144H), 7.58 -7.74 (m, 54H); ^{13}C {^{1}H} NMR (75 MHz, CD_2Cl_2) δ 12.2, 23.4, 32.9 (d, *J* = 12.3 Hz, 2C), 34.1, 65.6, 66.1, 110.7, 121.2, 121.4 (d, *J* = 4.0 Hz), 121.71 (d, *J* = 4.0 Hz), 122.8, 126.9, 128.2, 128.3, 128.6, 130.0, 131.1, 132.2, 132.5, 133.7, 134.8, 138.9 (d, *J* =13.5 Hz), 139.3 (d, *J* = 13.5 Hz), 149.4 (d, *J* = 7.1 Hz), 150.1, 151.2 (d, *J* = 7.1 Hz, 2C), 155.3, 167.5, 195.4. Anal. Calcd for $C_{648}H_{600}Cl_{48}N_{39}O_{138}P_{21}S_{18}$: C, 55.31; H, 4.30; N, 3.88; found: C, 55.04; H, 4.28; N, 3.32.

***Synthesis of* 1-G3:**



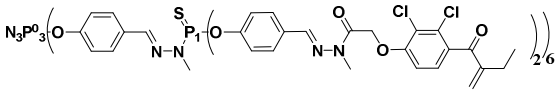
White solid, 85% yield (0.321 g). ^{31}P {^{1}H} NMR (121 MHz, CD_2Cl_2) δ 7.9 (s, P_0), 62.6 (s, P_1), 62.8 (s, P_2 and P_3). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.11 (t, *J* = 7.4 Hz, 144H), 2.42 (q, *J* = 7.4 Hz, 96H), 2.80-2.97 (m, 96H), 3.29 (d, *J* = 9.8 Hz, 126H), 4.26-4.45 (m, 96H), 4.69 (s, 96H), 5.55 (s, 48H), 5.92 (s, 48H), 6.70 (d, *J* = 8.5 Hz, 48H), 7.02-7.29 (m, 324H), 7.69 (d large, 126H). ^{13}C {^{1}H} NMR (75 MHz, CD_2Cl_2) δ 12.2, 23.4, 32.9 (d, *J* = 12.6 Hz, 3C), 34.1, 65.6, 66.1, 110.7, 121.2, 121.4 (d, *J* = 4.5 Hz), 121.8 (s, 2C), 122.8, 126.9, 128.2 (s, 2C), 128.3, 128.5, 130.0, 131.1, 132.4 (s, 2C), 133.6, 134.8 (s, 2C), 138.9 (d, *J* = 13.5 Hz), 139.3 (d, *J* = 13.5 Hz, 2C), 149.4 (d, *J* = 7.1 Hz, 2C), 150.1, 151.3 (d, *J* = 6.9 Hz, 2C), 155.3, 167.5, 195.4.M.W.29274.63. Anal. Calcd for $C_{1344}H_{1248}Cl_{96}N_{87}O_{282}P_{45}S_{42}$: C, 55.14; H, 4.30; N, 4.16; found: C, 54.81; H, 4.12; N, 3.89.

***Synthesis of* 2-Gn:**

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 the appropriate masses of phenol **EA-4** (300 mg, 0.687 mmol, n = 1), (228 mg, 0.525 mmol, n = 2) or (210 mg, 0.48 mmol, n = 3), and cesium carbonate (430 mg, 1.32 mmol, n = 1), (328 mg, 1.01 mmol, n = 2), (312 mg, 0.96 mmol, n = 3), were added. The reaction mixture was stirred overnight at room temperature, and then centrifuged to remove salts. The solution was concentrated and precipitated two times in pentane/Et_2O (9/1). The product was filtered and dried under vacuum to give **2-G1** (generation 1), **2-G2** (generation 2) or **2-G3** (generation 3) as white powders.

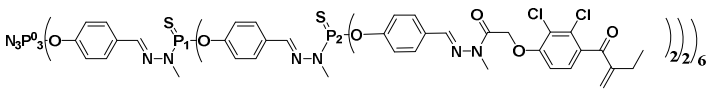
***Synthesis of* 2-G1:**



White solid, 88% yield (0.411 g). ^{31}P {^{1}H} NMR (162 MHz, CD_2Cl_2) δ 8.81 (s, P_0), 62.24 (s, P_1). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.12 (t, *J* = 7.4 Hz, 36H), 2.43 (q, *J* = 7.4 Hz, 24H), 3.27 (d, *J* = 10.1 Hz, 18H), 3.34 (s, 36H), 5.31 (s, 24H), 5.60 (s, 12H), 5.91 (s, 12H), 6.75 (d, *J* = 8.7 Hz, 12H), 6.88 (d, *J* = 8.5 Hz, 12H), 7.05 (d, *J* = 8.6 Hz, 12H), 7.22 (d, *J*

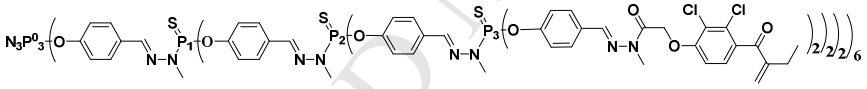
= 7.9 Hz, 24H), 7.55 (d, *J* = 8.5 Hz, 12H), 7.57 (d, *J* = 7.9 Hz, 24H), 7.63 (s, 6H), 7.67 (s, 1H). ^{13}C {^{1}H} NMR (75 MHz, CD_2Cl_2) δ 12.4, 23.4, 28.1, 32.9 (d, *J* = 11.8 Hz), 67.5, 111.1, 121.4, 121.7 (d, *J* = 4.5 Hz), 123.1, 126.7, 128.3, 128.5, 128.7, 131.1, 131.5, 132.1, 133.2, 138.9 (d, *J* = 14.8 Hz), 139.2, 150.1, 150.8-151.4 (m, C), 151.7 (d, *J* = 7.1 Hz), 156.1, 167.9, 195.9. Anal. Calcd for $C_{300}H_{276}Cl_{24}N_{39}O_{54}P_9S_6$: C, 54.48; H, 4.21; N, 8.26; S, 2.91; found: C, 54.20; H, 4.06; N, 7.98.

***Synthesis of* 2-G2:**



White solid, 85% yield (0.355 g). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 8.55 (s, P_0), 62.28 (s, P_2), 62.59 (s, P_1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, *J* = 7.4 Hz, 72H), 2.41 (q, *J* = 7.1 Hz, 48H), 3.19 (d, *J* = 9.8 Hz, 18H), 3.23-3.40 (m, 108H), 5.31 (s, 48H), 5.57 (s, 24H), 5.89 (s, 24H), 6.74 (d, *J* = 8.6 Hz, 24H), 6.88 (d, *J* = 8.1 Hz, 12H), 7.04 (d, *J* = 8.6 Hz, 24H), 7.13 (d, *J* = 7.9 Hz, 24H), 7.21 (d, *J* = 8.0 Hz, 48H), 7.53 (d, *J* = 8.0 Hz, 12H) 7.53-7.65 (m, 90H), 7.66 (s, 24H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 12.4, 23.4, 28.1, 32.1-33.7 (m, 2C), 67.5, 110.7, 121.2, 121.6, 121.8 (d, *J* = 3.6 Hz), 122.9, 126.8, 128.3 (s, 2C), 128.5, 128.7, 131.1, 131.4, 132.1, 132.3, 133.2, 139.0, 139.1, 139.3, 150.0, 151.3 (d, *J* = 7.2 Hz, 2C), 151.7 (d, *J* = 7.2 Hz), 156.1, 167.4, 195.9. Anal. Calcd for $C_{648}H_{600}Cl_{48}N_{87}O_{114}P_{21}S_{18}$: C, 54.20; H, 4.21; N, 8.49; found: C, 54.04; H, 3.97; N, 8.15.

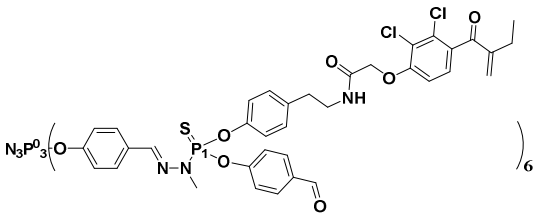
***Synthesis of* 2-G3:**



White solid, 85% yield (0.351 g). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 7.88 (s, P_0), 62.56 (s, P_1), 62.27 (s, P_2), 61.76 (s, P_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, *J* = 7.1 Hz, 144H), 2.27-2.47 (m, 48H), 3.11-3.42 (m, 270H), 5.28 (s, 96H), 5.52 (s, 24H), 5.84 (s, 24H), 6.71 (d, *J* = 8.4 Hz, 48H), 6.99 (d, *J* = 8.2 Hz, 60H), 7.11 (d, *J* = 6.4 Hz, 84H), 7.18 (d, *J* = 7.2 Hz, 96H), 7.44-7.71 (m, 262H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 12.4, 23.4, 28.1, 32.7-33.2 (m, 3C), 67.5, 111.7, 121.8 (s, 5C), 122.9, 126.8, 128.3 (s, 3C), 128.5, 128.7, 131.0, 131.4, 132.2, 132.3 (s, 2C), 133.1, 138.9-139.3 (m, 3C), 139.4, 150.0, 150.9-151.4 (m, 3C), 151.7 (d, *J* = 7.2 Hz), 156.1, 167.8, 195.9. Anal. Calcd for $C_{1344}H_{1248}Cl_{96}N_{183}O_{234}P_{45}S_{42}$: C, 54.08; H, 4.21; N, 8.59; found: C, 53.28; H, 3.86; N, 8.19.

***Synthesis of 3-G1*:**

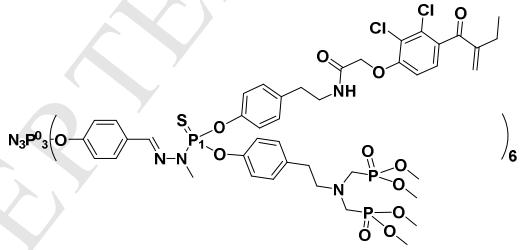
To a mixture of dendrimer **G1** (100 mg, 0.055 mmol) and cesium carbonate (215 mg, 0.66 mmol) in THF (20 mL), six equivalents of phenol **EA-2** (140 mg, 0.33 mmol) were added. The reaction mixture was stirred at room temperature overnight and monitored with ^{31}P NMR. When the monosubstitution was achieved, six equivalents of 4-hydroxybenzaldehyde (40 mg, 0.33 mmol) and cesium carbonate (215 mg, 0.66 mmol) were added. Again the reaction mixture was stirred at room temperature overnight. Salts were then removed by centrifugation and the clear solution was concentrated under reduced pressure. The residue was then dissolved in a minimum amount of THF (4 mL) and precipitated with a mixture of pentane/Et_2O (9:1) to afford **3-G1** as a white powder in 75 % yield.



White solid, 75% yield (0.340 g). ^{31}P {^{1}H} NMR (121 MHz, CD_2Cl_2) δ 8.3 (s, P_0), 61.69 (s, P_1), 62.87 (P_1, dis). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.15 (t, J = 7.4 Hz, 18H), 2.46 (q, J = 7.4 Hz, 12H), 2.83 (t, J = 6.6 Hz, 12H), 3.33 (d, J = 10.4 Hz, 18H), 3.58 (q, J = 6.6 Hz, 12H), 4.53 (s, 12H), 5.58 (s, 6H), 5.97 (s, 6H), 6.79 (s, 6H), 6.87 (d, J= 8.6 Hz, 6H), 7.05 (d, J = 8.5 Hz, 12H), 7.11-7.23 (m, 30H), 7.36 (d, J = 7.6 Hz, 12H), 7.62 (d, J = 8.5 Hz, 12H), 7.68 (s, 6H), 7.81 (d, J= 7.6 Hz, 12H), 9.90 (s, 6H). ^{13}C {^{1}H} NMR (75 MHz, CD_2Cl_2) δ 12.2, 23.4, 32.9 (d, J = 12.4 Hz), 34.9, 39.9, 68.2, 111.0, 121.2, 121.4 (d, J = 4.6 Hz), 121.9 (d, J = 4.9 Hz), 122.7, 127.3, 128.2, 128.7, 129.9, 130.9, 131.2, 132.1, 133.62, 133.9, 136.2, 139.2 (d, J = 14.3 Hz), 149.1 (d, J = 7.1 Hz), 150.1, 151.3, 154.5, 155.2 (d, J = 7.1 Hz), 166.4, 190.6, 195.3. Anal. Calcd for $C_{216}H_{198}Cl_{12}N_{21}O_{42}P_9S_6$: C, 55.71; H, 4.29; N, 6.32; found: C, 55.26; H, 4.11; N, 6.05.

***Synthesis of 4-G1*:**

To a mixture of dendrimer **G1** (100 mg, 0.055 mmol) and cesium carbonate (215 mg, 0.66 mmol) in THF (20 mL), six equivalents of phenol **EA-2** (140 mg, 0.33 mmol) were added. The reaction mixture was stirred at room temperature overnight and monitored with ^{31}P NMR. When the mono substitution was achieved, six equivalents of **1** (126 mg, 0.33 mmol) and cesium carbonate (215 mg, 0.66 mmol) were added. Again the reaction mixture was stirred at room temperature overnight. Salts were then removed by centrifugation, and the clear solution was concentrated under reduced pressure. The residue was dissolved in a minimum amount of THF (4 mL) and then precipitated with a mixture of pentane/Et_2O (9:1) to afford **4-G1** as a white powder in 65% yield.



White solid, 65% yield (0.525 g). ^{31}P {^{1}H} NMR (121 MHz, CD_2Cl_2) δ 8.3 (s, P_0), 26.5 (s, PO_3Me_2), 62.8 (P_1, dis), 63.1 (s, P_1). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.14 (t, J = 7.3 Hz, 18H), 2.45 (q, J = 7.3 Hz, 12H), 2.70-2.87 (m, 24H), 3.03 (t, J = 7.4 Hz, 12H), 3.16 (d, J = 9.3 Hz, 24H), 3.29 (d, J = 10.1 Hz, 18H), 3.56 (q, J = 6.5 Hz, 12H), 3.70 (d, J = 10.5 Hz, 72H), 4.53 (s, 12H), 5.58 (s, 6H), 5.97 (s, 6H), 6.79-6.93 (m, 12H), 6.99-7.25 (m, 66H), 7.60-7.72 (m, 18H). ^{13}C {^{1}H} NMR (75 MHz, CD_2Cl_2) δ 12.0, 23.2, 32.2, 32.8 (d, J = 12.4 Hz), 34.7, 40.0, 49.1 (dd, J = 157.5Hz, J = 8.2Hz), 52.0 (d, J = 6.9 Hz), 58.1 (t, J = 7.6Hz), 68.3, 111.8, 121.0 (d, J = 4.3 Hz), 121.20 (d, J = 4.4 Hz), 121.3, 122.1, 127.4, 128.3 (s, 2C), 129.9, 130.1, 130.2, 132.6, 133.5, 136.5, 137.3, 139.3 (d, J = 11.3 Hz), 148.9 (d, J = 6.8 Hz), 149.3 (d, J = 7.0 Hz), 150.1, 151.3, 155.3, 166.4, 194.9. Anal. Calcd for $C_{258}H_{312}Cl_{12}N_{27}O_{72}P_{21}S_6$: C, 49.89; H, 5.06; N, 6.09; found: C, 49.22; H, 4.99; N, 5.95.

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