Polish J. Chem., **78**, 75–82 (2004)

Synthesis of New Trifunctional Ligands Based on 1,4,7,10-Tetraazacyclododecane

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(Received July 14th,2003; revised manuscript September 25th, 2003)

Synthesis of 1,4,7,10-tetraazacyclododecanes with different N-substituents: chelating groups, fluorescent, and long lipophilic chain with ω-hydroxyl group is reported.

Key words: 1,4,7,10-tetraazacyclododecane, cyclen, light harvesting group

Interest in lanthanide complexation chemistry has increased rapidly over the past several years. In medicine gadolinium complexes are used as contrast agents in magnetic resonance imaging [1,2]. Luminescent lanthanide complexes are used as markers in the analysis of biological materials [3,4]. The design and synthesis of luminescent systems that exhibit large differences between their "off" (non emission) and "on" (emission) states is an active area of research within the field of supramolecular chemistry [5]. Examples include simple host-guest complexes as well as more advanced switches [6], grids [7], shuttles [8] and molecular machines [9]. Mimicking of the zero-one function of logic gates used in contemporary computers is of particular interest [10]. It had been described that quinolyl derived 1,4,7,10-tetraazacyclododecane Tb(III) complexes yield such logic gate (Figure 1) [11].

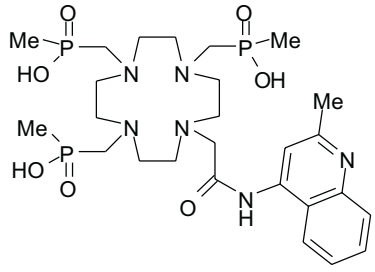

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Figure 1.

Such switches are also the basis of luminescent chemosensors for the recognition of physiologically important ions and molecules [12]. The use of that type of detection has several advantages over, for example, electrochemically based systems, since luminescent sensors give rise to non-invasive, real-time and on-line monitoring [13]. 1,4,7,10-Tetraazacyclododecane derivatives had been found as very

useful chelating reagents for transition metal and lanthanide cations. Direct alkylation of one equivalent of cyclen with four equivalents of electrophile allowed to introduce four identical coordinating pendant arms in one step reaction [14–17]. Selective high yield N-functionalization of 1,4,7,10-tetraazacyclododecane as a rule requires using protecting groups and the total synthesis consists of three reaction: protection of three nitrogen atoms; alkylation of the remaining free nitrogen atom, and deprotection [18–20]. N-Functionalization of cyclen that provides to tri- and tetra-functional derivatives is even more complicated and still presents a synthetic challenge.

RESULTS AND DISCUSSION

The aim of this work was the synthesis of cyclenes, containing three different substituents: chelating groups, fluorescent, and long lipophilic chain with ω-hydroxyl group (Figure 2).

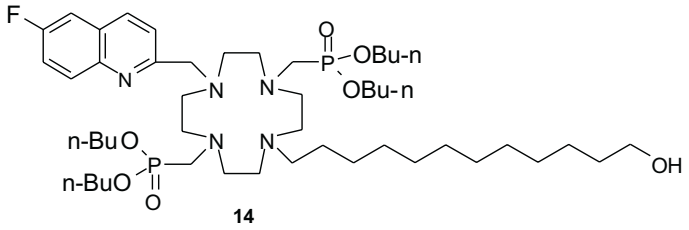

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Figure 2.

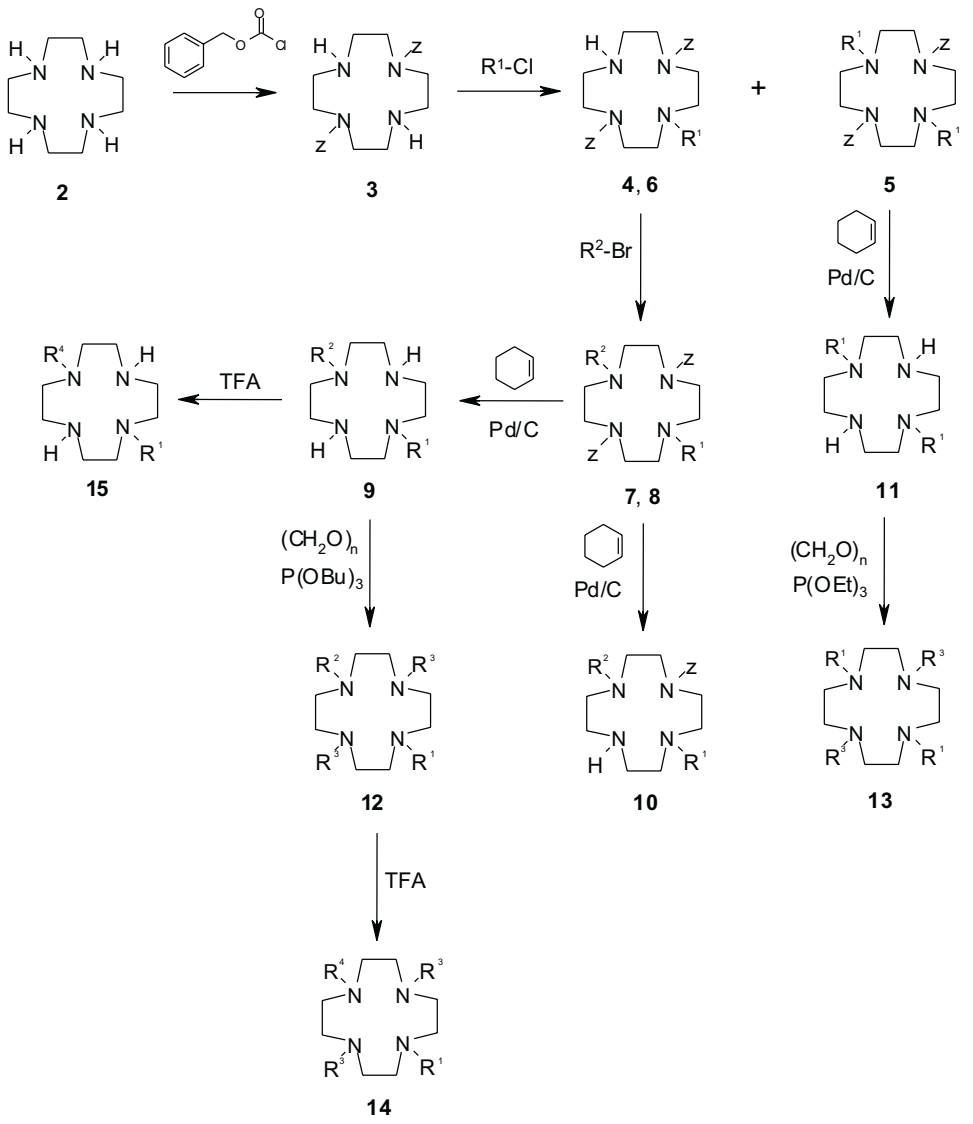
Such alcohols potentially can be used for modification of silylated silica gel [21] or glass; the OH group can be also exchanged for another substituents.

We used benzyl chloroformate to protect cyclen **2** in 1 and 7 position. It has been found that 1,4,7,10-tetraazacyclododecane reacts with chloroformates in acidic solution to give high yield of 1,7-diprotected derivative **3** [22]. The very high regioselectivity probably reflects the protonation sequence of the cyclen, having two very basic and two very acidic nitrogens, so the protonation of two nitrogens takes place in position as far away from each other as possible [23,24]. The benzyloxycarbonyl group is stable under basic conditions but it is easily removable by hydrochloric acid or by catalytic hydrogenation. Compound **3** was alkylated with 2-chloromethylene-6-fluoroquinoline [25] or 9-chloromethylenephenanthrene [26] (Scheme 1).

In the first case two products **4** and **5** are formed [27]. In the second case only monosubstituted product **5** was obtained with 80% yield. Probably, products distribution depends on the size of electrophile. The steric hindrance of bulky methylenephenanthrenyl group is considerable and only monosubstitution takes place.

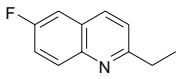
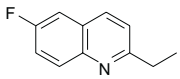
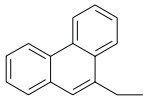
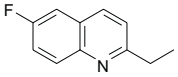
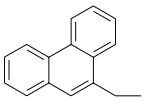
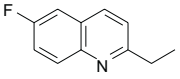
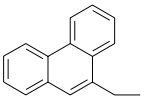
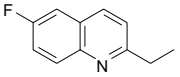
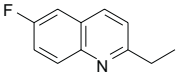
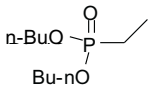
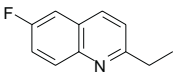
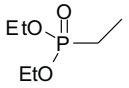
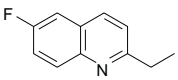
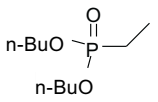
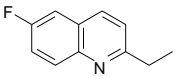
Compounds **4** and **6** have been further used for alkylation with 1-bromo-12-tetrahydropyranyloxydodecane in dry CH_3CN in the presence of anhydrous $NaHCO_3$

Scheme 1



(Scheme 1 and Table 1). Surprisingly, the yield of products was not as high as expected (57% and 48%, respectively). For instance 1-bromoethane allowed to obtain relative products with 70% yield. Efforts to improve the yield by using different solvents (acetonitrile, methanol, ethanol and DMF) or bases ($NaHCO_3$, Na_2CO_3, NaOH, NaH) and addition of KI were ineffective. Probably, the molecular structure made difficult free N atom to be attacked by the electrophile. The resulting compound **7** has been deprotected by catalytic hydrogen transfer using 10% Pd/C in anhydrous ethanol with cyclohexene as the hydrogen donor to give **9** with 70% yield.

Table 1. Synthesized 1,4,7,10-tetraazacyclododecane derivatives.

Compound	R^1	R^2	R^3	R^4	Z
3	–	–	–	–	$PhCH_2OOC$-
4		–	–	–	$PhCH_2OOC$-
5		–	–	–	$PhCH_2OOC$-
6		–	–	–	$PhCH_2OOC$-
7		THP-O$(CH_2)_{12}$-	–	–	$PhCH_2OOC$-
8		THP-O$(CH_2)_{12}$-	–	–	$PhCH_2OOC$-
9		THP-O$(CH_2)_{12}$-	–	–	–
10		THP-O$(CH_2)_{12}$-	–	–	$PhCH_2OOC$-
11		–	–	–	–
12		THP-O$(CH_2)_{12}$-		–	–
13		–		–	–
14		–		$HO(CH_2)_{12}$-	–
15		–	–	$HO(CH_2)_{12}$-	–

THP – tetrahydro-2*H*-pyran

Analogously was carried out deprotection of compound **5** and **8**. The catalytic hydrogen transfer has been found more effective then typical catalytic hydrogenation for several derivatives of cyclen [27]. In our case this procedure allowed us to remove both benzyloxycarbonyl groups from compound **7** and **5** but only one from derivative **8**. Use of a large excess of catalyst and cyclohexene to remove the second protective group was also unsuccessful.

Compounds **9** and **11** have been modified in reaction with paraformaldehyde and trialkyl phosphite. This one pot reaction introduced two phosphonic acid esters groups attached to cyclen at 4 and 10 position through methylene spacer. Finally, the protecting tetrahydropyranyl group was selectively removed from compounds **9** and **12** with trifluoroacetic acid (TFA) at room temperature.

In conclusions, we have presented here a simple way for the synthesis of trifunctional cyclen derivatives. This process allows the use of different alkylating agents in three consecutive alkylating steps. All obtained compounds have light harvesting moieties for efficient lanthanide sensitization. Additionally, the nitrogen of the 6-fluoroquinaldine moiety can act as a proton acceptor. These compounds have been found to display greater selectivity towards some of transition metal and lanthanide ions. Further work concerning all these aspects is currently in progress.

EXPERIMENTAL

All solvents were of HPLC grade and were used without further purification. Preparative chromatography of organic compounds was performed using flash chromatography (Merck Grade 60, 230–400 mesh silica gel, 60Å). ^{1}H NMR and ^{31}P NMR spectra were recorded at 500 MHz and 202.4 MHz, respectively. ^{1}H NMR spectra were complicated for benzyloxycarbonyl tetraazacyclododecanes because of hindered rotation about N–CO_2Bz bonds; purity and identity of these compounds was additionally checked by ^{13}C NMR (125 MHz). Analytical thin layer chromatography was carried out on Merck silica gel 60 F_{254} plates, and the spots were located with UV light or iodine vapors. Column chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04–0.06 mm). Drying of organic extracts during the work-up of reaction mixtures was performed over anhydrous $MgSO_4$, unless otherwise stated. Mass spectra LR and HR were obtained in positive ion mode using LSIMS(+), EI or ESI on AMD 604. 2-Chloromethylene-6-fluoroquinoline, 9-chloromethylenephenanthrene and 1,7-bis(benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane were obtained according to literature [22,25,26]. 1,4,7,10-Tetraazacyclododecane was purchased from Strem Co. (France).

1,7-Bis(benzyloxycarbonyl)-4-(6-fluoro-2-quinolinylmethyl)-1,4,7,10-tetraazacyclododecane (4) and 1,7,-bis(benzyloxycarbonyl)-4,10-(6-fluoro-2-quinolinylmethyl)-1,4,7,10-tetraazacyclododecane (5). The mixture of 1,7-bis(benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane **3** (3.3 g, 7.5 mmol), 2-chloromethyl-6-fluoroquinoline (1.46 g, 7.5 mmol) and anhydrous $NaHCO_3$ (0.63 g, 7.5 mmol) in anhydrous MeCN (400 mL) was stirred at 40°C for 48 hours. Then the insoluble inorganic salts were filtered off. The remaining solution was evaporated and the residue was purified by column chromatography. Product **5** was eluted with $CHCl_3$, then product **4** was eluted with $CHCl_3$: CH_3OH : 25% NH_3 aq. (40:1:1). Removal of the solvents under reduced pressure gave monosubstituted **4** and disubstituted **5** products as colorless oils. Yield of compound **4** – 1.85 g (64%) and compound **5** – 0.8 g (14%). ^{1}H NMR, ^{13}C NMR and MS of derivatives **4** and **5** identical to literature data [27].

1,7-Bis(benzyloxycarbonyl)-4-(9-phenathrenylmethyl)-1,4,7,10-tetraazacyclododecane (6). This compound was prepared from 1,7-bis(benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane **3** (3.3 g, 7.5 mmol) and 9-chloromethylphenanthrene (1.61 g, 7.5 mmol) by the former procedure. The desired

product **6** was obtained as colorless oil. Yield 3.78 g (80%). ^{1}H NMR ($CHCl_3$): δ 2.92–2.95 (m, 4H), 3.07–3.12 (m, 5H), 3.41–3.71 (m, 8H), 4.17 (s, 2H), 4.54 (s, 2H), 4.62 (s, 2H), 6.93–7.06 (m, 4H), 7.14–7.17 (m, 2H), 7.20–7.48 (m, 4H), 7.60–7.68 (m, 6H), 7.82–7.94 (m, 1H), 8.60–8.73 (m, 2H). ^{13}C NMR ($CHCl_3$): δ 46.57, 47.31, 48.78, 49.46, 54.37, 54.82, 55.26, 55.51, 56.10, 67.31, 122.47, 123.13, 123.71, 126.79, 127.43, 127.99, 128.27, 128.72, 129.25, 130.44, 130.89, 131.64, 132.12, 135.65, 156.61. Mass spectrum (ESI): $(M+H)^+$ 631; HRMS [ESI, $(M+H)^+$] calculated for $C_{39}H_{43}N_4O_4$: 631.3279; found 631.3262.

1,7-Bis(benzyloxycarbonyl)-4-(6-fluoro-2-quinolinylmethyl)-10-(12-tetrahydro-2*H*-pyranoxydodecane)-1,4,7,10-tetraazacyclododecane (7). To a mixture of 1,7-bis(benzyloxycarbonyl)-4-(6-fluoro-2-quinolinylmethyl)-1,4,7,10-tetraazacyclododecane **4** (1.63 g, 2.72 mmol) and $NaHCO_3$ (0.23 g, 2.73 mmol) in dry CH_3CN (20 mL) 1-bromo-12-tetrahydropyranyloxydodecane (0.95 g, 2.72 mmol) was added. The mixture was stirred at 60°C for 48 hours. Inorganic salts were filtered off. The solvent was removed under vacuum. The crude product was dissolved in CH_2Cl_2 and purified by column chromatography using $CHCl_3$: MeOH : 25% NH_3 (40:1:1). Fractions containing the product were combined and evaporated to give product **7** as colorless oil. Yield 1.35 g (57%). ^{1}H NMR ($CHCl_3$): δ 1.23–1.40 (m, 16H), 1.45–1.63 (m, 10H), 1.70–1.75 (m, 1H), 1.81–1.85 (m, 1H), 2.38–2.50 (m, 2H), 2.57–2.80 (m, 8H), 3.36–3.40 (m, 1H), 3.41–3.63 (m, 8H), 3.64–3.71 (m, 1H), 3.86–3.89 (m, 1H), 3.90 (s, 2H), 4.79 (s, 2H), 5.09 (s, 2H), 6.85–6.98 (m, 2H), 7.02–7.14 (m, 4H), 7.29–7.49 (m, 8H), 7.91–8.02 (m, 1H). ^{13}C NMR ($CHCl_3$): δ 19.97, 25.74, 26.49, 27.00, 28.04, 29.74, 29.84, 29.94, 30,00, 31.04, 44.88, 46.13, 48.84, 54.48, 55.35, 55.91, 56.80, 61.62, 62.62, 67.18, 67.94, 99.11, 110.89, 119.37 (d, J_{C-F} = 25.75 Hz), 122.06, 127.97, 128.12, 128.40, 128.81, 131.42, 135.74, 136.47, 144.75, 156.63, 160.32 (d, J_{C-F} = 247,75 Hz), 160.69. Mass spectrum (LSIMS(+)) $(M+H)^+$ 868, $(M+Na)^+$ 890; HRMS [LSIMS(+), $(M+H)^+$] calculated for $C_{51}H_{71}FN_5O_6$: 868.5388; found 868.5368.

1,7-Bis(benzyloxycarbonyl)-4-(9-phenanthrenylmethyl)-10-(12-tetrahydro-2*H*-pyranoxydodecane)-1,4,7,10-tetraazacyclododecane (8). According to the general procedure compound **8** was prepared from 1,7-bis(benzyloxycarbonyl)-4-(9-phenanthrenylmethyl)-1,4,7,10-tetraazacyclododecane **6** (1.89 g, 3 mmol) and 1-bromo-12-tetrahydropyranyloxydodecane (0.96 g, 3 mmol). Colorless oil. Yield 1.25 g, (48%). ^{1}H NMR ($CHCl_3$): δ 1.27–1.37 (m, 16H), 1.47–1.62 (m, 8H), 1.71–1.76, (m, 1H), 1.83–1.87 (m, 1H), 2.44–2.69 (m, 6H), 2.70–2.85 (m, 4H), 3.38–3.43 (m, 4H), 3.51–3.56 (m, 6H), 3.74–3.78 (m, 1H), 3.88–3.91 (m, 1H), 4.08 (s, 2H), 4.56–4.59 (m, 1H), 4.76 (s, 2H), 5.03 (s, 2H), 6.88–6.98 (m, 2H), 7.01–7.06 (m, 4H), 7.25–7.34 (m, 4H) 7.55–7.62 (m, 5H), 7.70 (s, 1H), 7.73–7.88, (m, 1H), 8.65–8.72 (m, 2H). ^{13}C NMR ($CHCl_3$): δ 19.98, 25.77, 26.52, 27.99, 29.77, 29.89, 29.98, 30,03, 31.06, 48.23, 54.20, 55.07, 62.63, 67.19, 67.97, 99.12, 122.65, 123.16, 126.49, 126.59, 127.98, 128.08, 128,33, 128.69, 128.69, 130.86, 131.93, 133.24, 133.34, 136.66, 156.86. Mass spectrum (ESI) $(M+H)^+$ calculated for $C_{56}H_{75}N_4O_6$: 899.57; found 899.

1-(6-Fluoro-2-quinolinylmethyl)-7-(12-tetrahydro-2*H*-pyranoxydodecane)-1,4,7,10-tetraazacyclododecane (9). Product **7** (1.25 g 1.44 mmol) was dissolved in anhydrous ethyl alcohol and 10% Pd/C catalyst (1 g), and cyclohexene (2 mL) were added. The mixture was refluxed for three days. After cooling the catalyst was filtered through Celite, then the filtrate was concentrated under vacuum producing slightly yellow viscous oil. The crude product was then purified by column chromatography $CHCl_3$: CH_3OH : 25 % NH_3 aq. (10:1:1) to give compound **9** as colorless oil. Yield 0.60 g (70%). ^{1}H NMR ($CHCl_3$): δ 1.24–1.40 (m, 16H), 1.48–1.63 (m, 8H), 1.68–1.73 (m, 1H), 1.82–1.84 (m, 1H), 2.45 (t, J = 7.3, 2H), 2.53–2.74 (m, 18H), 3.35–3.39 (m, 1H), 3.47–3.51 (m, 1H), 3.70–3.74 (m, 1H), 3.84–3.89 (m, 1H), 3.91 (s, 2H), 4.56–4.57 (m, 1H), 7.37 (dd, J_1= 2.7 Hz, J_2 = 8.8 Hz, 1H), 7.45 (ddd, J_1 = 2.7 Hz, J_2 = 8.9 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 8.01 (dd, J_1 = 5.2 Hz, J_2 = 8.9 Hz, 1H), 8.04 (d, J = 8.9 Hz 1H). Mass spectrum (ESI) $(M+H)^+$ 600; HRMS [ESI, $(M+H)^+$] calculated for $C_{35}H_{59}FN_5O_2$: 600.4653; found 600.4675.

1-(Benzyloxycarbonyl)-4-(9-phenanthrenylmethyl)-10-(12-tetrahydro-2*H*-pyranoxydodecane)-1,4,7,10-tetraazacyclododecane (10). This compound was prepared from 1,7-bis(benzyloxycarbonyl)-4-(9-phenanthrenylmethyl)-10-(12-tetrahydropyranyloxydodecane)-1,4,7,10-tetraazacyclododecane **8** (0.87 g 1 mmol) by the former procedure. The product **10** was obtained as colorless oil. Yield 0.57 g

(75%). ^{1}H NMR ($CHCl_3$): δ 1.23–1.37 (m, 16H), 1.55–1.61 (m, 8H), 1.71–1.75 (m, 1H), 1.82–1.88 (m, 1H), 2.28–2.32 (m, 2H), 2.55–2.59 (m, 5H), 2.71–2.77 (m, 4H), 2.84–2.87 (m, 4H), 3.20–3.24 (m, 4H), 3.38–3.42 (m, 1H), 3.50–3.52 (m, 1H), 3.72–3.77 (m, 1H), 3.88–3.90 (m, 1H), 4.11 (s, 2H), 4.57–4.60 (m, 1H), 4.95 (s, 2H), 7.18–7.22 (m, 2H), 7.23–7.30,(m, 3H), 7.56–7.59 (m, 1H), 7.61–7.66 (m, 3H), 7.70 (s, 1H), 7.82–7.83 (m, 1H), 8.17–8.29 (m, 1H), 8.65–8.72 (m, 2H). ^{13}C NMR ($CHCl_3$):δ 19.98, 25.74, 26.52, 27.68, 28.19, 29.78, 29.88, 30.02, 31.04, 44.81, 54.12, 54.56, 60.57, 62.65, 67.44, 67.98, 99.13, 122.76, 123.37, 125.20, 126.86, 127.02, 128.35, 128,63, 128.69, 128.86, 130.86, 131.93, 133.24, 133.34, 136.24, 156.28. Mass spectrum (ESI) $(M+H)^+$ calculated for $C_{48}H_{69}N_4O_4$: 765.53; found 765.

1,7-Bis(6-fluoro-2-quinolinylmethyl)-1,4,7,10-tetraazacyclododecane (11). This compound was prepared from 1,7-bis(benzyloxycarbonyl)-4,10-bis(6-fluoro-2-quinolinylmethyl)-1,4,7,10-tetraazacyclododecane **5** (0.76 g 1 mmol) using 10% Pd/C (0.5 g) as catalyst and cyclohexene (3 mL) by the previous procedure. The amorphous colorless product **11** was obtained with 0.32 g (65%) yield. ^{1}H NMR ($CHCl_3$):δ 2.57–3.95 (m, 18H), 3.96 (s, 4H), 7.42 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 2H), 7.46 (ddd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 8.03–8.07 (m, 4H). ^{1}H NMR ($CHCl_3$ + D_2O): δ 2.70 (s, 16H), 3.95 (s, 4H), 7.42 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 2H), 7.46 (ddd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 8.04–8.07 (m, 4H). Mass spectrum (LSIMS(+)) $(M+H)^+$ 491, $(M+Na)^+$ 513; HRMS [LSIMS(+), $(M+Na)^+$] calculated for $C_{28}H_{32}F_2N_6Na$: 513.2554; found 513.2552.

1-(6-Fluoro-2-quinolinylmethyl)-7-(12-tetrahydro-2*H*-pyranoxydodecane)-1,4,7,10-tetraazacyclododecane-4,10-bis(methanephosphonic acid dibutyl ester) (12). Paraformaldehyde (0.038 g, 1.26 mmol) was added to a mixture of tetraazacyclododecane **9** (0.36 g, 0.6 mmol) and triethyl phosphite (0.25 mL, 1.44 mmol). The mixture was stirred at room temperature for 5 days. The resulting clear oil was loaded on silica gel column and product was eluted with $CHCl_3$: CH_3OH: 25% NH_3 (40:1:1). The fractions containing the product were combined and the solvents were removed under vacuum to give the product **12** as colorless oil. Yield 0.30 g (58%). ^{1}H NMR ($CHCl_3$): δ 0.92 (t, J = 7.3 Hz, 12) 1.22–1.30 (m, 16H), 1.32–1.36 (m, 8H), 1.51–1.62 (m, 16H), 1.69–1.75 (m, 1H), 1.80–1.87 (m, 1H), 2.69–2.79 (m, 6H), 2.84–2.94 (m, 12H), 2.95–3.19 (m, 4H), 3.36–3.42 (m, 1H), 3.48–3.54 (m, 1H), 3.71–3.79 (m, 1H), 3.84–3.92 (m, 1H), 3.92–4.02 (m, 10H), 4.59 (t, J = 2.9 Hz, 1H), 7.41 (dd, J_1 = 2.4 Hz, J_2 = 8.3 Hz, 1H), 7.46 (ddd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 7.82 (d J =8.3 Hz, 1H), 8.22 (dd, J_1 = 5.4 Hz, J_2 = 8.8 Hz, 1H), 8.07 (d J = 8.3 Hz, 1H). ^{31}P NMR ($CHCl_3$/H_3PO_4): δ 27.34, 27.39. Mass spectrum (LSIMS(+)) $(M+H)^+$ 1012, $(M+Na)^+$ 1034; HRMS [LSIMS(+), $(M+Na)^+$] calculated for $C_{53}H_{96}FN_5O_8P_2$ Na: 1034.6615; found 1034.6607

1,7-Bis(6-fluoro-2-quinolinylmethyl)-1,4,7,10-tetraazacyclododecane-4,10-bis(methanephosphonic acid diethyl ester) (13). Paraformaldehyde (0.044 g, 1.45 mmol) was added to a mixture of 1,7-bis(6-fluoro-2-quinolinylmethyl)-1,4,7,10-tetraazacyclododecane **11** and triethyl phosphite (0.29 mL, 1.66 mmol). The mixture was stirred at room temperature for 6 days. The resulting clear oil was loaded on silica gel column and the product was eluted with $CHCl_3$: CH_3OH : 25% NH_3 (40:1:1) to give product **13** as colorless oil. Yield 0.33 g (60%). ^{1}H NMR ($CHCl_3$): δ 1.21 (t, J = 7.32 Hz, 12H) 2.82–2.93 (m, 10H), 2.94–2.96 (m, 10H) 3.95–4.05 (m, 12H), 7.43 (dd, J_1 = 2.9 Hz, J_2 = 8.8 Hz, 2H), 7.46 (ddd, J_1 = 2.9 Hz, J_2 = 8.8 Hz, 2H), 7.89 (d J =8.3 Hz, 2H), 8.05 (dd, J_1 = 5.4 Hz, J_2 = 9.3 Hz, 2H), 8.10 (d J = 8.3 Hz, 2H). ^{31}P NMR ($CHCl_3$/H_3PO_4): δ 25.91, 25.96. Mass spectrum (ESI) $(M+H)^+$ 791; HRMS [ESI, $(M+H)^+$] calculated for $C_{38}H_{55}F_2N_6O_4P_2$: 791.3626; found 791.3602.

1-(6-Fluoro-2-quinolinylmethyl)-7-(12-hydroxydodecane)-1,4,7,10-tetraazacyclododecane-4,10-bis(methanephosphonic acid dibutyl ester) (14). 1-(6-Fluoroquinolinylmethyl)-7-(12-tetrahydropyranyloxydodecane)-1,4,7,10-tetraazacyclododecane-4,10-bis(methanephosphonic acid dibutyl ester) **12** (0.24 g, 0.22 mmol) was dissolved in TFA (2 mL). The solution was left at room temperature for 1 hour. The excess of TFA was removed under reduce pressure. The residue was dissolved in diethyl ether and washed with 5% NaOH solution (2 mL). The organic layer was dried with anhydrous Na_2SO_4 and evaporated under vacuum to give product **14** as colorless oil. Yield 0.20 g (93%). ^{1}H NMR ($CHCl_3$): δ 0.94 (t, J = 7.3 Hz, 12H), 1.20–1.31 (m, 24H), 1.30–1.38 (m, 8H), 1.41–1.46 (m, 2H), 1.49–1.57 (m, 2H), 2.62, (t, J = 7.3 Hz, 2H), 2.70–2.76, (m, 4H), 2.87, (d, J = 9.3 Hz, 4H), 2.91–2.94 (m, 8H), 2.96–3.04 (m, 4H), 3.48 (t, J = 5.2 Hz, 2H), 3.71–3.79 (m, 1H), 3.90–4.03 (m, 10H), 7.38 (dd, J_1 = 2.4 Hz, J_2 = 8.3 Hz,

1H), 7.47 (ddd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 7.81 (d J =8.3 Hz, 1H), 8.20 (dd, J_1 = 5.4 Hz, J_2 = 8.8 Hz,1H), 8.04 (d, J = 8.3, 1H). ^{31}P NMR ($CHCl_3/H_3PO_4$): δ 27.30, 27.41. Mass spectrum (ESI) $(M+H)^+$ 928; HRMS [ESI, $(M+H)^+$] calculated for $C_{48}H_{89}FN_5O_7P_2$: 928.6621; found 928.6640.

1-(6-Fluoro-2-quinolinylmethyl)-7-(12-hydroxydodecane)-1,4,7,10-tetraazacyclododecane (15). This compound was prepared from 1-(6-fluoro-2-quinolinylmethyl)-7-(12-tetrahydropyranyloxydodecane)-1,4,7,10-tetraazacyclododecane **9** (0.30 g , 0.5 mmol) by the previous procedure. Colorless oil. Yield 0.24 g (95%). ^{1}H NMR ($CHCl_3$): δ 1.24–1.32 (m, 16H), 1.43–1.51 (m, 4H), 2.42 (t, J = 7.3 Hz, 2H), 2.52–2.54 (m, 4H), 2.58–2.62 (m, 4H), 2.63–2.70 (m, 8H), 2.98 (s, 3H), 3.45–3.49 (m, 2H), 3.89 (s, 2H), 7.36 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz 1H), 7.42 (ddd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.99–8.03 (m, 2H). Mass spectrum (ESI) $(M+H)^+$ 516; HRMS [ESI, $(M+H)^+$] calculated for $C_{30}H_{51}FN_5O$: 516.4078; found 516.4057.

Acknowledgments

This work was supported by DS No 014668/003. The author is indebted to Professor J.F. Biernat for valuable discussion and his assistance in preparation of this manuscript. The author gratefully acknowledges graduate students D. Pokropska and A. Graczyk for their contributions in compounds preparation.

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