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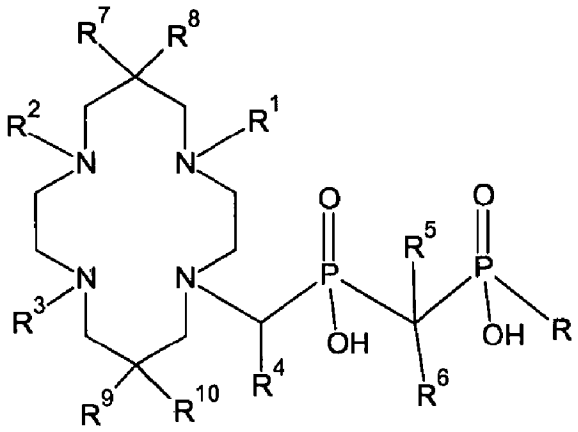
(54) Title: CYCLAM BASED COMPOUNDS, THEIR CONJUGATES, CO-ORDINATION COMPOUNDS, PHARMACEUTICAL COMPOSITION CONTAINING THEREOF, METHOD OF PREPARATION AND USE THEREOF



(I)

(57) Abstract: Cyclam based compounds, their conjugates, co-ordination compounds, pharmaceutical composition containing thereof, method of preparation and use thereof The present invention relates to cyclam based compounds of the general formula (I), conjugates of such compounds with conjugation groups, their coordination compounds, targeting conjugates, method of preparation of cyclam based compounds, intermediate products for the preparation of cyclam based compounds, a pharmaceutical preparation containing them, and the use thereof.

Cyclam based compounds, their conjugates, co-ordination compounds, pharmaceutical composition containing thereof, method of preparation and use thereof

Field of Art

The present invention relates to cyclam based compounds, containing tetraazamacrocycle and bis-phosphorus acid, conjugates of such compounds with conjugation groups, their coordination compounds, targeting conjugate, method of preparation of cyclam based compounds, intermediate products for the preparation of cyclam based compounds, pharmaceutical preparation containing them, and the use thereof.

Background Art

Polyazamacrocycles with coordinating side chains form thermodynamically very stable complexes with a wide scale of metal ions that are often also highly kinetically inert. These properties thereof are very desirable for applications in medicine and molecular biology. Therefore, these ligands and complexes thereof are widely studied and their properties adapted to a particular application, as for example MRI contract agents, carriers for metal radionuclides in diagnostic or therapeutic methods, targeted medicaments or luminescent probes.

Very powerful diagnostic methods of modern medicine are positron emission tomography (PET) or tomographic scintigraphy (single-photon emission tomography, SPECT), which are based on the application of radio-isotopes, i.e. proton-rich isotopes of elements that undergo β^+ decay (for PET), or emitting gamma radiation (for SPECT). In PET, a collision of emitted positron with electron from the surrounding tissue leads to origination of a pair of collinear γ-photons (having the energy of 512 keV), which allow a precise detection of place of annihilation thus also the distribution of the radio-isotope in the body. PET requires using radio-isotopes with suitable half-life, low energy of emitted positrons and good availability (for example non-metallic radio-isotopes ^{18}F, ^{11}C, ^{15}O, or radioisotopes of metals, such as ^{68}Ga, ^{44}Sc, ^{89}Zr). Great interest was raised up by the radioisotope of copper ^{64}Cu (61 % β^+) thanks to its long half-life ($\tau_{½}$ 12.8 h) and low energy of positrons (E_{av} 0.65 MeV), which leads to a high resolution in PET. Further radioisotopes of copper, positron emitting ^{60}Cu ($\tau_{½}$ 23.7 min, 100 % β^+) and ^{61}Cu ($\tau_{½}$ 3.3 h, 100 % β^+), are also used in PET, and the β^--emitting ^{67}Cu ($\tau_{½}$ 61.8 h, 100 % β^-) is used

in radionuclide therapy. Radio-isotopes ^{64}Cu and ^{67}Cu form an interesting theranostic pair (one isotope is used for diagnostics and the second isotope for therapy).

Radioisotopes of metals mostly cannot be applied in a form of free ions because of non-specific accumulation in tissues. In order to achieve the required bio-distribution, the metal ion shall be bound in a thermodynamically stable and kinetically inert complex, and this complex is often conjugated to the targeting vector. There are various chelators for a formation of thermodynamically stable and kinetically inert complexes of metals, while the macrocyclic ligands are preferred. For the complexation of copper radioisotopes, both acyclic and macrocyclic ligands are used, for example diethylenetriaminepentaacetic acid (H_5dtpa), 1,4,8,11-tetraazacyclotetradecane (cyclam), 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid (H_4teta), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (H_4dota), their monoamides and other derivatives. However, their properties are not optimal for complexation of copper(II) ions, especially because of a slow complexation, low kinetic inertness, and unsuitable redox potential shifted towards copper(I) ions, and, therefore, other ligands were studied, for example derivatives of bridged cyclam, which form kinetically very inert complexes, however, they are burdened by a very slow complexation.

Preparation of various macrocyclic ligands on the basis of cyclen (1,4,7,10-tetraazacyclododecane) or cyclam (1,4,8,11-tetraazacyclotetradecane), with a pendant group containing phosphorus or eventually arsenic, is described for example in US 2008/0312430 A1 or WO2015/038968. The document Fuzerová S., Kotek J., Císařová I., Hermann P., Binnemans K, Lukeš I., *Dalton Trans.*, **2005**, 2908–2915, describes the synthesis, the potentiometric and NMR titrations, and the crystallographic structure of a ligand on the basis of cyclam with a pendant phosphonic acid and its copper(II) complexes. The document Kotek J., Lubal P., Hermann P., Císařová I., Lukeš I., Godula T., Svobodová I., Táborský P., Havel J., *Chem. Eur. J.*, 2003, **9**, No. 1, 233–248, describes an analogous compound, which, however, contains two pendant phosphonic acids in a trans position. This publication also studies the synthesis, potentiometry, and crystallographic study of the ligand and its copper complexes. It results from the two last mentioned documents that one phosphonic acid group is coordinated to Cu^{II} and it forms a thermodynamically stable and kinetically inert complex. The second phosphonic acid group present in the compound studied in Kotek J., Lubal P., Hermann P., Císařová I., Lukeš I., Godula T., Svobodová I., Táborský P., Havel J., *Chem. Eur. J.*, 2003, **9**, No. 1, 233–248 does not coordinate to the copper(II) ion and the thermodynamic stability of

copper(II) complexes of both ligands mentioned above is comparable. The cited compounds, however, are not bifunctional, they cannot thus be linked to any targeting vector in order to get to a specific place in the body during biodistribution. Moreover, although the substances cited form stable copper complexes, the complexation rate is not sufficient for that the resulting complex to be created quickly and, if possible, at room temperature. Thus, for the practical use in radiodiagnostics or radiotherapy, these substances are not suitable because of their non-selective biodistribution and low complexation rate.

For targeted biodistribution and dosage reduction, the conjugation of a complex with a targeting vector is used. Targeting vectors may be, for example, various peptides, antibodies and their fragments or derivatives, biotin, folic acid, cyclodextrins, dendrimers, polymers, polysaccharides.

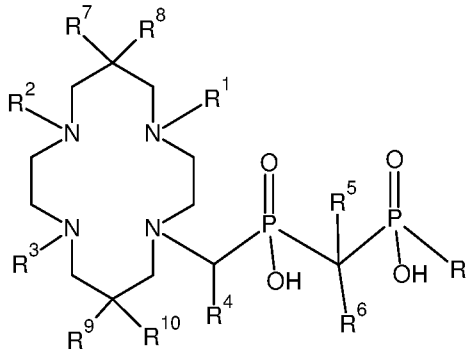
The disadvantage of the prior art is the absence of substances with high specific activity, which is a value indicating the percentage representation of the complex of the radioisotope in the total dose of the medicament. This value is closely related with the capability of ligands to form a thermodynamically stable and kinetically inert coordination compound with radionuclide, with a suitable half-life, quickly and, if possible, at room temperature, which would, at the same time, contain a targeting vector, and therefore would be suitable for applications in diagnostic (for example PET, SPECT) and therapeutic methods. The existing ligands effectively complex radionuclides at temperatures of approximately 80 °C and higher, while at room temperature their complexation is very slow, which causes, for example, loss of radioisotope complexes with a short half-life, high financial costs associated with preparation of radioisotope complexes, as well as the stress of the patient exposed to an application of high doses of the medicament in order to achieve the desired effect.

Disclosure of Invention

The present invention relates to compounds based on cyclam and/or bridged cyclam for therapy and diagnostics, containing a bis-phosphorus acid, which are characterized by a high specific activity. The compounds according to the present invention complex metal ions quickly and selectively, in particular Cu^{2+} ions, and they form thermodynamically stable and kinetically inert coordination compounds. The compounds according to the present invention may further form conjugates with conjugation groups and further

targeting conjugates with targeting vectors that ensure their targeted distribution in the organism.

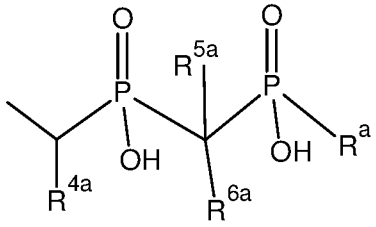
The subject of the present invention are cyclam based compounds for therapy and diagnostics of the general formula **(I)**



(I)

wherein

R, R^a, R^1, R^2, R^3 are independently selected from the group comprising H, OH, (C1 to C6)alkyl, which may be linear or branched, (C3 to C6)cycloalkyl, benzyl, and/or R^1 and/or R^2 and/or R^3 is a bis-phosphorus acid of the general formula **(II)**

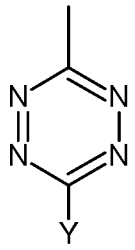


(II)

and/or R^1 and R^3 together form (C2 to C3)alkylene, which may be substituted with one or more linear or branched (C1 to C6)alkyls,

and/or R, R^a are independently selected from phenyl and (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O,

wherein the (C1 to C6)alkyl, (C3 to C6)cycloalkyl, phenyl, benzyl and (C5 to C6) heterocycle, containing at least one heteroatom of N, S, O, may be independently substituted with one or more groups selected from COOH; NH_2; NO_2, NX_2; $C(O)NX_2$; NHX; C(O)NHX; OH; SH; -NCS; tetrazine of the general formula **(III)**;



(III)

(C7 to C8)cycloalkenyl in *trans* configuration, which may eventually be further substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; norbornenyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; $-N_3$; (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O; (C2 to C6)alkynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2,-NCS, -NCO, N_3 and SH; cyclooctynyl, eventually substituted with one or more groups chosen from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; cycloazaoctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; maleimide; phenyl; benzyl and -P(O)(OH)Z;

and wherein R^4, R^{4a}, R^5 and R^{5a} are independently H, (C1 to C6)alkyl, which may be linear or branched, (C3 to C6)cycloalkyl, benzyl;

wherein (C1 to C6)alkyl, (C3 to C6)cycloalkyl and benzyl may be independently substituted with one or more groups selected from COOH; NH_2; NO_2, NX_2; $C(O)NX_2$; NHX; C(O)NHX; OH; SH; -NCS; tetrazine of the general formula (**III**); (C7 to C8)cycloalkenyl in *trans* configuration, which may eventually be further substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; norbornenyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; $-N_3$; (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O; (C2 to C6)alkynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; cyclooctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; cycloazaoctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; maleimide; phenyl; benzyl and -P(O)(OH)Z;

and wherein R^6 and R^{6a} is H;

and wherein R^7, R^8, R^9 and R^{10} are independently selected from the group comprising H, (C1 to C6)alkyl, (C3 to C6)cycloalkyl, benzyl, phenyl, NO_2, COOH, (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O, and/or altogether R^7 and R^8 contain (C2 to C3)alkylene or vinylene and/or altogether R^9 and R^{10} contain (C2 to C3)alkylene or vinylene,

wherein (C1 to C6)alkyl, (C3 to C6)cycloalkyl, phenyl, benzyl, (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O, (C2 to C3)alkylene and vinylene may be independently substituted with a group or groups selected from COOH; NH_2; NO_2; NX_2; $C(O)NX_2$; SH; tetrazine of the general formula (**III**); (C7 to C8)cycloalkenyl in *trans* configuration, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; norbornenyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; -N_3; (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O; (C2 to C6)alkynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; cyclooctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; cycloazaoctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; maleimide; phenyl; benzyl and –P(O)(OH)Z,

wherein Y is H, (C1 to C6)alkyl, $–CH_2COOH$, (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O, or heteroaryl, containing at least one heteroatom of N, S, O, preferably Y is an atom of hydrogen, methyl or pyridyl;

wherein Z is H; OH; (C1 to C6)alkyl, which may be linear or branched; (C1 to C6)hydroxyalkyl; (C1 to C6)alkoxyl; phenyl; (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O; or benzyl, wherein phenyl, (C5 to C6)heterocycle or benzyl may eventually be substituted with one or more groups selected from COOH, NH_2, NO_2, N_3 and SH, preferably the substituent is in *para* position;

and wherein X is independently H; (C1 to C6)alkyl, which may be linear or branched; (C3 to C6)cycloalkyl; phenyl and/or benzyl;

while for X, Y and Z applies, that (C1 to C6)alkyl, (C3 to C6)cycloalkyl, phenyl and/or benzyl may be independently substituted with one or more groups selected from COOH; NH_2; NO_2, NX_2; $C(O)NX_2$; NHX; C(O)NHX; SH; tetrazine of the general formula (**III**); (C7 to C8)cycloalkenyl in *trans*

configuration, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; norbornenyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; $-N_3$; (C2 to C6)alkynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; cyclooctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; cycloazaoctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; maleimide; phenyl; benzyl and -P(O)(OH)Z;

wherein at least one of the groups R, R^a, R^1, R^2, R^3, R^4, R^{4a}, R^5, R^{5a}, R^6, R^{6a}, R^7, R^8, R^9 a R^{10} contains at least one of the groups -COOH; NH_2; NO_2, NX_2, NHX; C(O)NHX; N_3; SH; -NCS; tetrazine of the general formula (**III**); (C7 to C8)cycloalkenyl in *trans* configuration, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, N_3 and SH; norbornenyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, N_3 and SH; $-N_3$; (C2 to C6)alkynyl; cyclooctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, N_3 and SH; cycloazaoctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, N_3 and SH; maleimide; phenyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, N_3 and SH; benzyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, N_3 and SH; (C1 to C6)alkyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, N_3 and SH; and -P(O)(OH)Z.

In one embodiment of the invention, R^1 and R^3 together form (C2 to C3)alkylene, which may be substituted with (C1 to C6)alkyl, which may be linear or branched.

In another embodiment of the invention, R, R^a, R^1, R^2, R^3, R^4, R^{4a}, R^5, R^{5a}, R^6 and R^{6a} are independently selected from the group comprising H; (C1 to C6)alkyl, which may be linear or branched; (C3 to C6) cycloalkyl; benzyl; phenyl; (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O;

and/or R^1 and/or R^2 and/or R^3 is the bis-phosphorus acid of the general formula **(II)**, preferably at least one of the groups R^1, R^2 and R^3 is the bis-phosphorus acid of the general formula **(II)**, most preferably R^2 is the bis-phosphorus acid of the general formula **(II)**.

In one preferred embodiment, R^2 is selected from the group comprising H; (C1 to C6)alkyl, which may be linear or branched; (C3 to C6)cycloalkyl; benzyl; phenyl; (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O; and bis-phosphorus acid of the general formula **(II)**.

In another preferred embodiment, the cyclam-based compounds according to the present invention are selected from the group comprising compounds of the general formula **(I)**, whose the substituents are represented in the following combinations:

Compound number	R	R^1	R^3	R^2	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}
1	H	H	H	H	CH_3	H	H	H	H	H	H
2	H	CH_3	CH_3	CH_3	CH_3	H	H	H	H	H	H
3	H	CH_3	CH_3	H	H	H	H	H	H	H	H
4	H	CH_3	CH_3	CH_3	H	H	H	H	H	H	H
5	OH	benzyl	benzyl	H	H	H	H	H	H	H	H
7	OH	H	benzyl	benzyl	H	H	H	H	H	H	H
8	*p*-nitrobenzyl	H	H	H	H	H	H	H	H	H	H
9	*p*-aminobenzyl	H	H	H	H	H	H	H	H	H	H
10	*p*-SCN-benzyl	H	H	H	H	H	H	H	H	H	H
11	*p*-azidobenzyl	H	H	H	H	H	H	H	H	H	H
12	$-CH_2N(Bz)_2$	H	H	H	H	H	H	H	H	H	H
13	$-CH_2NH_2$	H	H	H	H	H	H	H	H	H	H
14	$-(CH_2)_2COOH$	H	H	H	H	H	H	H	H	H	H
15	H	H	H	H	H	$-(CH_2)_4COOH$	H	H	H	H	H

16	H	H	H	H	H	H	H	CH_3	NO_2	NO_2	CH_3
22	H	CH_3	CH_3	acid of formula (**II**), wherein R^a = R, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
23	$-(CH_2)_2COOH$	CH_3	CH_3	acid of formula (**II**), wherein R^a = R, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
24	OH	benzyl	benzyl	$-CH_2P(O)(OH)_2$	H	H	H	H	H	H	H
25	OH	H	H	$-CH_2P(O)(OH)_2$	H	H	H	H	H	H	H
26	OH	$-CH_2P(O)(OH)_2$	benzyl	benzyl	H	H	H	H	H	H	H
27	OH	$-CH_2P(O)(OH)_2$	H	H	H	H	H	H	H	H	H
28	H	$-(CH_2)_2-$		H	H	H	H	H	H	H	H
29	OH	$-(CH_2)_2-$		H	H	H	H	H	H	H	H
30	H	$-(CH_2)_2-$		H	CH_3	H	H	H	H	H	H
31	*p*-nitrobenzyl	$-(CH_2)_2-$		H	H	H	H	H	H	H	H
32	H	$-(CH_2)_2-$		acid of formula (**II**), wherein R^a = R, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
33	$-CH_2OH$	$-(CH_2)_2-$		acid of formula (**II**), wherein R^a = R, R^{4a} to R^{6a}	H	H	H	H	H	H	H

			= H							
34	OH	$-(CH_2)_2-$	acid of formula (**II**), wherein R^a = R, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
35	$-(CH_2)_2COOH$	$-(CH_2)_2-$	acid of formula (**II**), wherein R^a = R, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
36	H	$-(CH_2)_2-$	acid of formula (**II**), wherein R^a = OH, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
37	*p*-nitrobenzyl	$-(CH_2)_2-$	acid of formula (**II**), wherein R^a = OH, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
38	*p*-aminobenzyl	$-(CH_2)_2-$	acid of formula (**II**), wherein R^a = OH, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
39	*p*-SCN-benzyl	$-(CH_2)_2-$	acid of formula (**II**), wherein R^a = OH, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
40	*p*-azidobenzyl	$-(CH_2)_2-$	acid of formula (**II**),	H	H	H	H	H	H	H

				wherein R^a = OH, R^{4a} to R^{6a} = H								
41	*p*-nitrobenzyl	-$(CH_2)_2$-		–$CH_2P(O)(OH)(CH_2OH)$	H	H	H	H	H	H	H
42	*p*-nitrobenzyl	-$(CH_2)_2$-		–$CH_2P(O)(OH)_2$	H	H	H	H	H	H	H
43	*p*-aminobenzyl	-$(CH_2)_2$-		–$CH_2P(O)(OH)_2$	H	H	H	H	H	H	H
50	H	–$(CH_2)_2$–		H	H	–$(CH_2)_4CH_3$	H	H	H	H	H
51	H	–$(CH_2)_2$–		2-picolyl-*N*-oxide	H	–$(CH_2)_4CH_3$	H	H	H	H	H
52	H	–$(CH_2)_2$–		–CH_2COOH	H	H	H	H	H	H	H
53	OH	–$(CH_2)_2$–		–$CH_2P(O)(OH)$–$(CH_2)_2COOH$	H	H	H	H	H	H	H
54	H	–CH_3	–CH_3	–$CH_2P(O)(OH)Ph$	H	H	H	H	H	H	H
55	*p*-nitrobenzyl	–$(CH_2)_2$–		–$CH_2P(O)(OH)$–$CH_2N(2\text{-picolyl})_2$	H	H	H	H	H	H	H
56	–$(CH_2)_2COOH$	H	H	H	–$(CH_2)_3N_3$	H	H	H	H	H	H
57	*p*-nitrobenzyl	–$(CH_2)_2$–		–$(CH_2)_2S$– (dimer)	H	H	H	H	H	H	H
58	H	H	H	H	H	H	H	-CH_3	-NH_2	-NH_2	-CH_3
59	*p*-nitrobenzyl	H	H	H	H	H	H	-COOH	H	H	H
60	*p*-nitrobenzyl	H	H	H	H	H	H	-$(CH_2)_2OH$	H	H	H
61	–$(CH_2)_2COOH$	H	H	H	H	H	H	*2*-pyridyl	H	*2*-pyridyl	H

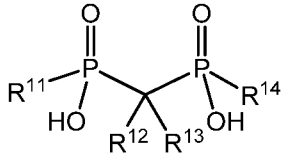
The subject of the present invention is also a conjugate of the cyclam-based compound according to the present invention and of at least one conjugation group, which is covalently bound to the cyclam-based compound, and which is selected from the group containing OH, -COOH; NH_2; NO_2, NX_2, NHX; C(O)NHX; N_3; SH; -NCS; tetrazine of the general formula (**III**); (C7 to C8)cycloalkenyl in *trans* configuration, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX; C(O)NHX; N_3 and SH; norbornenyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX; C(O)NHX; N_3 and SH; $-N_3$; (C2 to C6)alkynyl; cyclooctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX; C(O)NHX; N_3 and SH; cycloazaoctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, (C1 to C6)alkyl, (C6)aryl, N_3 and SH; maleimide; and -P(O)(OH)Z; wherein the conjugate may further contain a spacer between the cyclam-based compound and the conjugation group and/or between two conjugation groups, the spacer selected from the group containing (C1 to C6)*n*-alkyl, eventually substituted with C=O and/or -NH- group; phenylene; amino-acids chains with the length of 1 to 5 amino-acids; polyethylene glycols of 1 to 10 monomeric units.

The subject of the present invention are also coordination compounds of the cyclam based compounds of the general formula (**I**) or the conjugates according to the present invention, with metal cations selected from the group consisting of Cu^{2+}, Bi^{3+}, lanthanide cations, Sc^{3+}, Y^{3+}, Pb^{2+}, Zr^{4+}, Ac^{3+}, Mn^{2+} and Mn^{3+}, preferably lanthanide cations, Bi^{3+}, Y^{3+} a Cu^{2+}, more preferably Lu^{3+}, Bi^{3+}, Y^{3+} and Cu^{2+}. Metal cations may preferably be radioisotopes of metals, especially radioisotopes of copper, lutetium, bismuth, and yttrium.

The subject of the present invention is also a targeting conjugate, which contains the cyclam based compound of the general formula (**I**) and/or the conjugate and/or the coordination compound according to the present invention, and a targeting vector, selected from the group comprising bis(phosphonates); groups capable of fluorescence, for example fluoresceines, rhodamines or the boron-dipyrromethene (BODIPY) type substances, preferably emitting in the red or near infra-red (NIR) part of the spectrum, most preferably fluorescein and rhodamine; oligopeptides of 1 to 15 aminoacids; antibodies or fragments thereof, especially the Fab antigen binding fragments; folic acid;

biotin; compounds targeting to PSMA receptor, preferably urea derivatives or organo-phosphorous compounds; cyclodextrins; dendrimers, preferably PAMAM dendrimers; hydrophilic polymers on the basis of derivatives of acrylic acid, especially hydroxoalkylamides of acrylic acid, preferably hydroxoalkylamides of acrylic acid modified with amino groups and/or maleimido groups, most preferably the block copolymer of poly[*N*-(2-hydroxopropyl)methacrylamide and poly-L-lysine, poly[*N*-(2-hydroxopropyl)methacrylamide with free amino groups and poly[*N*-(2-hydroxopropyl)methacrylamide with free maleimide groups. Cyclodextrins, dendrimers and hydrophilic polymers based on derivatives of the acrylic acid are preferably modified with functional groups allowing for further conjugations of targeting vectors, serving thus for, not limited to, to increase the number of molecules of the compound of the general formula (**I**) in the targeting conjugate. Targeting conjugates containing Fab fragments of antibodies have, compared to the whole antibodies, faster pharmacokinetics in the organism, therefore, they are pharmacokinetically more preferred comparing to antibodies. Targeting conjugates containing groups capable of fluorescence are suitable especially for targeted image-guided surgery (IGS).

The subject of the present invention is also a method of preparation of cyclam based compounds of the general formula (**I**) according to the present invention, wherein the intermediate product of the general formula (**IV**),



(IV)

wherein R^{11}, R^{12}, R^{13} and R^{14} are in the following combinations:

Intermediate	R^{11}	R^{12}	R^{13}	R^{14}
A	H	H	H	OH
B	H	H	H	*p*-nitrobenzyl
C	H	H	H	$-CH_2N(benzyl)_2$
D	H	H	H	$-(CH_2)_2COOH$
E	H	$-(CH_2)_4COOH$	H	H
F	OH	$-(CH_2)_3NH$(4-dibenzylcyclooktyn	OH	OH

		amidobutoxyl)		

or a compound selected from the group containing methylene-bis(phosphinic acid), phosphorous acid, hydroxymethylphosphinic acid, reacts with a cyclam derivative and aldehyde in aqueous solution of an acid with the concentration within the range of from 10 to 40 % (weight), preferably from 18 to 36 % (weight), at the temperature in the range of from 40 °C to 80 °C for the period of time of at least 12 hours;
wherein the cyclam derivative is 1,4,8,11-tetraazacyclotetradecane and derivatives thereof and 1,4,8,11-tetraazabicyclo[6.6.2]hexadecane and derivatives thereof, preferably the cyclam derivative is selected from the group containing 1,4,8,11-tetraazacyclotetradecane, 1,4,8,11-tetraazabicyclo[6.6.2]hexadecane, 1,4,8-trimethyl-1,4,8,11-tetraazacyclotetradecane, 1,8-dimethyl-1,4,8,11-tetraazacyclotetradecane, 1,8-dibenzyl-1,4,8,11-tetraazacyclotetradecane, 1,4-dibenzyl-1,4,8,11-tetraazacyclotetradecane, 6,13-dimethyl-6,13-dinitro-1,4,8,11-tetraazacyclotetradecane; the aldehyde is selected from the group containing acetaldehyde, formaldehyde and para-formaldehyde, and the acid is preferably HCl and/or CF_3COOH; and wherein the reaction may be preceded by the step of preparation of the intermediate product.

In one embodiment of the method of preparation of the cyclam based compounds of the general formula **(I)** according to the present invention, the resulting product is further subjected to a reduction reaction. Preferably, the reduction reaction is performed as a hydrogenation in the presence of catalysts, reduction with hydride complexes, reduction with metals in acid solutions or using sulfides.

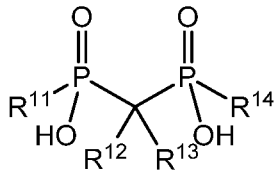
In another embodiment of the method of preparation of the cyclam based compounds of the general formula **(I)** according to the present invention, the resulting product is further subjected to an oxidation reaction. Preferably, the oxidation reaction is performed with oxidation agents selected from the group containing Cl_2, I_2 or Br_2 in water or in organic solvents, oxygen-containing oxidation agents, such as hydrogen peroxide or (organic) peroxoacids or salts thereof, metal ions in oxidation states capable of reduction, such as Hg^{2+} or Cu^{2+}, or (organic) oxoacids of iodine in high formal oxidation degrees of +III or +V.

In another embodiment of method of preparation of cyclam based compounds of the general formula **(I)** according to the present invention, the resulting product is further subjected to reaction with an aldehyde; and eventually with an intermediate product of the general formula **(IV)**, or with a compound, selected from the group containing methylene-bis(phosphinic acid), phosphorous acid, alkylphosphinic acid or arylphosphinic acid, preferably hydroxymethylphosphinic acid; in aqueous solution of an acid, preferably HCl or CF_3COOH.

In another embodiment of the method of preparation of cyclam based compounds of the general formula **(I)** according to the present invention, the reduction step is followed by a step when the product of the reduction undergoes a reaction with $CSCl_2$ or $COCl_2$.

In another embodiment of the method of preparation of cyclam based compounds of the general formula **(I)** according to the present invention, the reduction step is followed by a step when the resulting product of the reduction undergoes a reaction with NaN_3.

The subject of the present invention is also an intermediate product of the general formula **(IV)**,



(IV)

wherein R^{11}, R^{12}, R^{13} and R^{14} are in the following combinations:

Intermediate	R^{11}	R^{12}	R^{13}	R^{14}
B	H	H	H	*p*-nitrobenzyl
C	H	H	H	$-CH_2N(benzyl)_2$
D	H	H	H	$-(CH_2)_2COOH$
E	H	$-(CH_2)_4COOH$	H	H
F	OH	$-(CH_2)_3NH$(4-dibenzylcyclooktynamidobutoxyl)	OH	OH

The subject of the present invention is also a pharmaceutical preparation, which contains at least one cyclam based compound according to the present invention and/or at least one conjugate according to the present invention and/or at least one coordination compound according to the present invention and/or at least one targeting conjugate according to the present invention, and a pharmaceutically acceptable substance. The dosage form of the pharmaceutical preparation is a form for administration by injection, most often as a bolus or as an infusion, preferably intravenously. Suitable pharmaceutically acceptable auxiliary substances are preferably selected from the group containing solvents (especially aqueous or saline solution), buffers (especially phosphate buffer, HEPES = 2-[4-(2-hydroxyethyl)piperazine-1-yl]ethanesulfonic acid), ionization additives, antioxidants, antimicrobial additives. A person skilled in the art would be able, without exerting inventive activity, to determine which adjuvans to choose.

Subject of the present invention is also the cyclam based compound according to the present invention and/or at least one conjugate according to the present invention and/or at least one coordination compound according to the present invention and/or at least one targeting conjugate according to the present invention and/or the pharmaceutical preparation according to the present invention, for use as a medicament, preferably in the treatment of tumor diseases, inflammations, and/or atherosclerosis. Especially coordination compounds with metal radioisotopes according to the present invention, preferably with copper, lutetium, bismuth and yttrium radioisotopes, are suitable for the use as medicaments in radiotherapy. Cyclam based compounds according to the present invention were successfully tested *in vivo* in rodents. It results from the tests performed that those substances are neither deposited nor decomposed anywhere in the body and they are excreted from the body in a normal manner (urine, faeces). Therefore, they are suitable for medical applications.

The subject of the present invention is also the cyclam based compound according to any of the claims 1 thru 5 and/or at least one conjugate according to the present invention and/or at least one coordination compound according to the present invention and/or at least one targeting conjugate according to the present invention and/or the pharmaceutical preparation according to the present invention, for use as a contrast agent in medical diagnostics, preferably in the diagnostics of tumor diseases, inflammations, and/or atherosclerosis. For luminescence methods in medical diagnostics, coordination

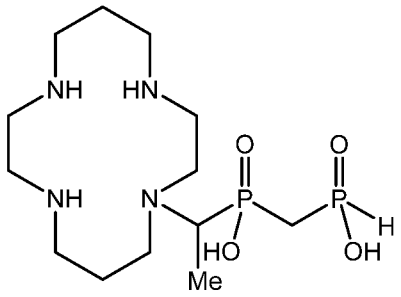
compounds according to the present invention containing cations of trivalent lanthanides are especially suitable; for magnetic nuclear resonance (NMR, MRI), coordination compounds of gadolinium are suitable.

The subject of the present invention is the use of cyclam based compounds according to the present invention and/or of the conjugate according to the present invention and/or of the coordination compound according to the present invention and/or of the targeting conjugate according to the present invention and/or of the pharmaceutical preparation according to the present invention, in radiochemistry as markers or precursors of markers when labelling with the use of radioisotopes of copper, lutetium, bismuth and yttrium, preferably using radioisotopes of copper, more preferably ^{64}Cu.

The subject of the present invention is the use of cyclam based compounds according to the present invention and/or of the conjugate according to the present invention and/or of the coordination compound according to the present invention and/or of the targeting conjugate according to the present invention, for the complexation and/or purification of copper radioisotopes.

Examples

Example 1: *Synthesis of compound* ***1***



To a glass vial (4 mL), 1,4,8,11-tetraazacyclotetradecane (205 mg; 1.02 mmol; 5.0 equiv.) was added. Methylene-bis(phosphinic acid) (85.6 mg; 594 μmol; 2.9 equiv.), acetaldehyde (9.0 mg; 205 μmol; 1.0 equiv.) and aqueous HCl (6 M; 2 mL) were subsequently added and the resulting suspension was stirred at 80 °C overnight. The mixture was evaporated to dryness and several times co-evaporated with H_2O. Crude product was purified by ion exchange chromatography (DOWEX 50; H^+-form; $H_2O \rightarrow$ 10% aqueous pyridine). The pyridine fraction with product was evaporated to dryness and further co-evaporated with H_2O (25 mL). The residue was re-dissolved in

H_2O (25 mL) and subsequently lyophilized. Product was obtained as white substance (35.0 mg; 40%; 1 step, based on acetaldehyde).

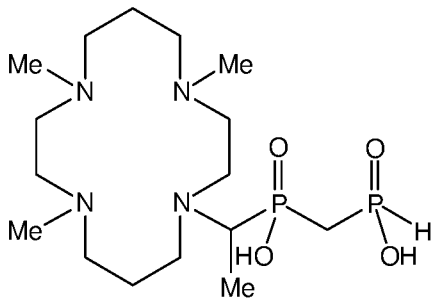
NMR (D_2O): **^{1}H** δ 1.16 (CH_3, dd, 3H, $^3J_{HP}$ = 15 Hz, $^2J_{HH}$ = 7 Hz); 1.73–2.00 (P—CH_2—P, CH_2—CH_2—CH_2, m, 5H); 2.08 (P—CH_2—P, dddd, 1H, $^2J_{HH}$ = 19 Hz, $^2J_{HP}$ = 16 Hz, $^2J_{HP}$ = 12 Hz, $^3J_{HH}$ = 4 Hz); 2.52–3.24 (CH_2—N, m, 16H); 3.37 (CH—CH_3, dq, 1H, $^2J_{HP}$ = 14 Hz, $^2J_{HH}$ = 7 Hz); 7.12 (PH, dd, $^1J_{HP}$ = 534 Hz, $^3J_{HH}$ = 4 Hz); **^{13}C**{^{1}H} δ 6.3 (CH_3, bm); 23.9 (CH_2—CH_2—CH_2, s); 26.2 (CH_2—CH_2—CH_2, s); 34.2 (P—CH_2—P, dd, $^1J_{CP}$ = 78 Hz, $^1J_{CP}$ = 73 Hz); 44.8 (*cycle*, s); 46.4 (*cycle*, s); 46.5 (*cycle*, s); 46.7 (*cycle*, s); 49.4 (*cycle*, s); 49.6 (*cycle*, d, $^3J_{CP}$ = 10 Hz); 50.0 (*cycle*, s); 50.6 (*cycle*, s); 52.0 (N—CH—P, d, $^1J_{CP}$ = 109 Hz); **^{31}P** δ 19.1 (*P*H, dtd, 1P, $^1J_{PH}$ = 534 Hz, $^2J_{PH}$ = 16 Hz, $^2J_{PP}$ = 4 Hz); 35.5 (N—CH—*P*, m, 1P).

MS: (−) 368.8 $[M-H^+]^-$. (+) 371.0 $[M+H^+]^+$; 392.9 $[M+Na^+]^+$; 408.9 $[M+K^+]^+$.

TLC (SiO_2, *i*-PrOH–conc. NH_4OH–H_2O 7:3:3): R_f = 0.7.

EA ($C_{13}H_{32}N_4O_4P_2 \cdot 3.5H_2O$, M_R = 433.4): C 36.0 (35.6); H 9.1 (8.9); N 12.9 (13.2).

Example 2: *Synthesis of compound* ***2***



To a glass vial (4 mL), tetrahydrochloride of 1,4,8-trimethyl-1,4,8,11-tetraazacyclotetradecane (65.2 mg; 168 μmol; 1.0 equiv.) was added. Methylene-bis(phosphinic acid) (73.2 mg; 508 μmol; 3.0 equiv.), acetaldehyde (8.1 mg; 184 μmol; 1.1 equiv.) and aqueous HCl (6 M; 2 mL) were subsequently added and the resulting suspension was stirred at 60 °C for two days. The mixture was evaporated to dryness and several times co-evaporated with H_2O. Crude product was purified by ion exchange chromatography (DOWEX 50; H^+-form; $H_2O \rightarrow$ 10% aqueous pyridine). The pyridine fraction with product was evaporated to dryness and further co-evaporated with H_2O (25 mL). The residue was re-dissolved in H_2O (55 mL) and subsequently lyophilized. Product was obtained as a white substance (48.7 mg; 63%; 1 step, based on acetaldehyde).

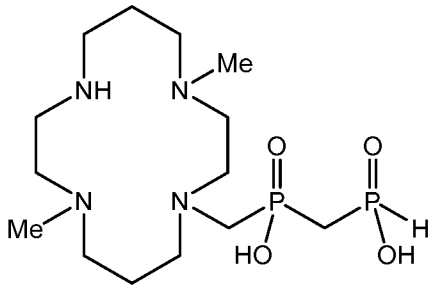
NMR (D_2O): **^{1}H** δ 1.19 (CH_3—C, dd, 3H, $^3J_{HP}$ = 16 Hz, $^2J_{HH}$ = 7 Hz); 1.68 (CH_2—CH_2—CH_2, m, 4H); 1.81 (P—CH_2—P, m, 1H); 1.98 (P—CH_2—P, m, 1H); 2.25 (CH_3—N, m, 3H); 2.27 (CH_3—N, s, 6H); 2.48–3.16 (CH_2—N, m, 16H); 3.41 (CH—CH_3, dq, 1H, $^2J_{HP}$ = 15 Hz, $^2J_{HH}$ = 7 Hz); 7.13 (P*H*, dm, $^1J_{HP}$ = 533 Hz); **^{13}C**{^{1}H} δ 7.1 (CH_3—C, s); 21.4 (CH_2—CH_2—CH_2, s); 22.7 (CH_2—CH_2—CH_2, s); 35.2 (P—CH_2—P, dd, $^1J_{CP}$ = 77 Hz, $^1J_{CP}$ = 73 Hz); 43.6 (CH_3—N, s); 43.7 (CH_3—N, s); 43.9 (CH_3—N, s); 46.2 (*cycle*, s); 48.2 (*cycle*, s); 50.0 (*cycle*, s); 50.8 (*cycle*, d, $^3J_{CP}$ = 8 Hz); 51.3 (*cycle*, d, $^3J_{CP}$ = 9 Hz); 51.9 (*cycle*, s); 53.5 (*cycle*, s); 53.6 (*cycle*, s); 56.5 (N—CH_2—P, d, $^1J_{CP}$ = 109 Hz); **^{31}P** δ 19.7 (*P*H, dtd, 1P, $^1J_{PH}$ = 533 Hz, $^2J_{PH}$ = 16 Hz, $^2J_{PP}$ = 3 Hz); 32.1 (N—CH—*P*, m, 1P).

MS: (−) 410.9 $[M-H^+]^-$. (+) 413.1 $[M+H^+]^+$; 435.1 $[M+Na^+]^+$; 451.0 $[M+K^+]^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 4:1): R_f = 0.3.

EA ($C_{16}H_{38}N_4O_4P_2 \cdot 2.5H_2O$, M_R = 457.4): C 42.0 (42.3); H 9.5 (9.1); N 12.3 (12.2).

Example 3: *Synthesis of compound* ***3***



To a glass flask (25 ml), tetrahydrochloride of 1,8-dimethyl-1,4,8,11-tetraazacyclotetradecane (1.56 mg; 4.17 mmol; 2.5 equiv.) was added. Methylene-bis(phosphinic acid) (480 mg; 3.33 mmol; 2.0 equiv.), paraformaldehyde (50 mg; 1.67 mmol; 1.0 equiv.) and aqueous HCl (6 M; 5 mL) were subsequently added and the resulting suspension was stirred at 80 °C overnight. The mixture was evaporated to dryness and several times co-evaporated with H_2O. Crude product was purified by ion exchange chromatography (DOWEX 50; H^+-form; $H_2O \rightarrow$ 10% aqueous pyridine). The pyridine fraction with product was evaporated to dryness and further co-evaporated several times with H_2O. The crude product was further purified by column chromatography (SiO_2; EtOH–conc. NH_4OH 4:1; R_f = 0.4). Fractions with product were combined and evaporated to dryness. The residue was suspended in H_2O (25 mL), treated with small amounts of charcoal and filtered through syringe microfilter (Millipore; 0.22 μm). The filtrate was re-purified by ion exchange chromatography (DOWEX 50; H^+-

form; $H_2O \rightarrow$ 10% aqueous pyridine). The pyridine fraction with product was evaporated to dryness and further co-evaporated several times with H_2O. The residue was re-dissolved in H_2O (25 mL) and subsequently lyophilized. Product was obtained as a white substance (215 mg; 29%; 1 step, based on paraformaldehyde).

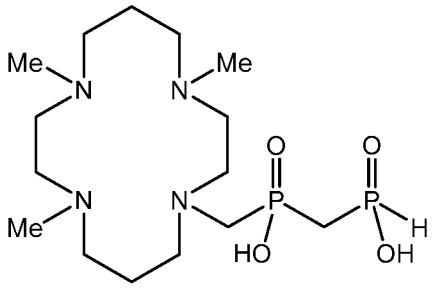
NMR (D_2O): **^{1}H** δ 1.70 (CH_2—C*H*$_2$—CH_2, p, 2H, $^3J_{HH}$ = 7 Hz); 1.76 (CH_2—C*H*$_2$—CH_2, p, 2H, $^3J_{HH}$ = 7 Hz); 2.03 (P—C*H*$_2$—P, ddd, 2H, $^2J_{HP}$ = 18 Hz, $^2J_{HP}$ = 16 Hz, $^3J_{HH}$ = 2 Hz); 2.24 (C*H*$_3$, s, 3H); 2.30 (C*H*$_3$, s, 3H); 2.50 (*cycle*, t, 2H, $^3J_{HH}$ = 7 Hz); 2.57 (*cycle*, m, 4H); 2.66 (*cycle*, t, 2H, $^3J_{HH}$ = 7 Hz); 2.69–2.82 (*cycle*, N—C*H*$_2$—P, m, 10H); 7.14 (P*H*, dt, $^1J_{HP}$ = 531 Hz, $^3J_{HH}$ = 2 Hz); **^{13}C**{^{1}H} δ 23.0 (CH_2—*C*H$_2$—CH_2, s); 23.6 (CH_2—*C*H$_2$—CH_2, s); 35.9 (P—*C*H$_2$—P, dd, $^1J_{CP}$ = 77 Hz, $^1J_{CP}$ = 75 Hz); 43.5 (*cycle*, s); 43.2 (*C*H$_3$, s); 43.8 (*C*H$_3$, s); 44.8 (*cycle*, s); 51.1 (*cycle*, d, $^3J_{CP}$ = 8 Hz); 52.2 (*cycle*, s); 53.1 (*cycle*, s); 53.4 (*cycle*, s); 53.5 (*cycle*, d, $^3J_{CP}$ = 6 Hz); 53.7 (*cycle*, s); 56.1 (N—*C*H$_2$—P, d, $^1J_{CP}$ = 109 Hz); **^{31}P** δ 19.8 (*P*H, dtd, 1P, $^1J_{PH}$ = 531 Hz, $^2J_{PH}$ = 18 Hz, $^2J_{PP}$ = 3 Hz); 32.5 (N—CH—*P*, m, 1P).

MS: (−) 382.6 [M−H$^+$]$^-$. (+) 384.6 [M+H$^+$]$^+$; 406.8 [M+Na$^+$]$^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 4:1): R_f = 0.4.

EA ($C_{14}H_{34}N_4O_4P_2 \cdot 3.5H_2O$, M_R = 447.5): C 37.6 (37.5); H 9.2 (9.0); N 12.5 (12.4).

Example 4: *Synthesis of compound* ***4***



To a glass vial (4 mL), tetrahydrochloride of 1,4,8-trimethyl-1,4,8,11-tetraazacyclotetradecane (37.8 mg; 99.7 μmol; 1.0 equiv.) was added. Methylene-bis(phosphinic acid) (55.6 mg; 386 μmol; 3.9 equiv.), paraformaldehyde (5.6 mg; 210 μmol; 2.1 equiv.) and aqueous HCl (6 M; 2 mL) were subsequently added and the resulting suspension was stirred at 60 °C for two days. The mixture was evaporated to dryness and several times co-evaporated with H_2O. The crude product was purified by ion exchange chromatography (DOWEX 50; H$^+$-form; $H_2O \rightarrow$ 10% aqueous pyridine). The pyridine fraction with product was evaporated to dryness and further co-evaporated with H_2O (25 mL). The residue was re-dissolved in H_2O (25 mL) and subsequently

lyophilized. Product was obtained as a white substance (35.4 mg; 82%; 1 step, based on paraformaldehyde).

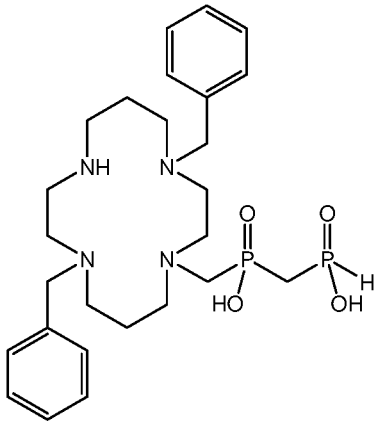
NMR (D_2O): **^{1}H** δ 1.71 (CH_2—CH_2—CH_2, m, 4H); 2.04 (P—CH_2—P, ddd, 2H, $^2J_{HP}$ = 18 Hz, $^2J_{HP}$ = 16 Hz, $^3J_{HH}$ = 2 Hz); 2.24 (CH_3, m, 6H); 2.27 (CH_3, s, 3H); 2.47–2.64 (*cycle*, m, 12H); 2.75 (*cycle*, m, 2H); 2.81 (N—CH_2—P, d, 2H, $^3J_{HH}$ = 9 Hz); 2.84 (*cycle*, m, 2H); 7.14 (P*H*, dt, $^1J_{HP}$ = 531 Hz, $^3J_{HH}$ = 2 Hz); **^{13}C**{^{1}H} δ 20.2 (CH_2—CH_2—CH_2, s); 20.6 (CH_2—CH_2—CH_2, s); 35.4 (P—CH_2—P, t, $^1J_{CP}$ = 77 Hz); 43.5 (CH_3, s); 43.7 (CH_3, s); 43.8 (CH_3, s); 49.0 (*cycle*, s); 49.2 (*cycle*, s); 49.6 (*cycle*, s); 50.0 (*cycle*, d, $^3J_{CP}$ = 8 Hz); 52.1 (*cycle*, d, $^3J_{CP}$ = 8 Hz); 52.2 (*cycle*, s); 53.4 (*cycle*, s); 53.5 (*cycle*, s); 56.7 (N—CH_2—P, d, $^1J_{CP}$ = 109 Hz); **^{31}P** δ 19.7 (*P*H, dtd, 1P, $^1J_{PH}$ = 531 Hz, $^2J_{PH}$ = 18 Hz, $^2J_{PP}$ = 3 Hz); 32.1 (N—CH—*P*, m, 1P).

MS: (−) 396.8 $[M-H^+]^-$. (+) 399.0 $[M+H^+]^+$; 421.0 $[M+Na^+]^+$; 437.0 $[M+K^+]^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 4:1): R_f = 0.2.

EA ($C_{14}H_{34}N_4O_4P_2 \cdot 2H_2O$, M_R = 434.5): C 41.5 (41.8); H 9.3 (9.1); N 12.9 (12.9).

Example 5: *Synthesis of compound* ***5***



To a glass vial (20 mL), tetrahydrochloride of 1,8-dibenzyl-1,4,8,11-tetraazacyclotetradecane (506 mg; 959 μmol; 2.0 equiv.) was added. Methylene-bis(phosphinic acid) (136 mg; 944 μmol; 2.0 equiv.). CF_3COOH (5 mL), aqueous HCl (12 M; 5 mL) and paraformaldehyde (20.9 mg; 474 μmol; 1.0 equiv.) were subsequently added and the resulting suspension was stirred at 80 °C for two days. The mixture was evaporated to dryness and several times co-evaporated with H_2O. The crude product was further purified by column chromatography (SiO_2; EtOH–conc. aq. NH_4OH 5:1; R_f = 0.6). The fractions with product were combined and evaporated to dryness. The residue was suspended in H_2O (25 mL), treated with small amounts of charcoal and filtered through

syringe microfilter (Millipore; 0.22 μm). The filtrate was re-purified by ion exchange chromatography (DOWEX 50; H^+-form; $H_2O \rightarrow$ 10% aqueous pyridine). The pyridine fraction with product was evaporated to dryness and further co-evaporated several times with H_2O. The residue was re-dissolved in H_2O (100 mL) and subsequently lyophilized. Product was obtained as a white substance (146 mg; 54%; 1 step, based on paraformaldehyde).

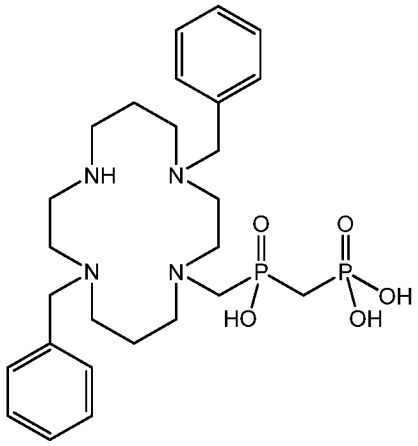
NMR (D_2O): δ 1.82 (CH_2—C*H*$_2$—CH_2, m, 4H); 2.05 (P—C*H*$_2$—P, dd, 2H, $^2J_{HP}$ = 18 Hz, $^2J_{HP}$ = 15 Hz); 2.46–2.61 (*cycle*, m, 6H); 2.74–3.12 (*cycle*, N—C*H*$_2$—P, m, 10H); 3.68 (C*H*$_2$—Ph, s, 2H); 3.75 (C*H*$_2$—Ph, s, 2H); 7.14 (P*H*, d, $^1J_{HP}$ = 529 Hz); 7.22–7.35 (*Ph*, m, 10H); **^{13}C**{^{1}H} δ 24.1 (CH_2—*C*H$_2$—CH_2, s); 27.2 (CH_2—*C*H$_2$—CH_2, s); 37.1 (P—*C*H$_2$—P, dd, $^1J_{CP}$ = 79 Hz, $^1J_{CP}$ = 71 Hz); 41.6 (*cycle*, s); 42.2 (*cycle*, s); 50.1 (*cycle*, d, $^3J_{CP}$ = 7 Hz); 52.2 (*cycle*, s); 53.3 (*cycle*, s); 53.4 (*cycle*, s); 53.8 (*cycle*, d, $^3J_{CP}$ = 9 Hz); 54,2 (*cycle*, s); 56.2 (*C*H$_2$—Ph, s); 58.8 (N—*C*H$_2$—P, d, $^1J_{CP}$ = 105 Hz); 59.1 (*C*H$_2$—Ph, s); 124.1 (*Ph*, s); 126.4 (*Ph*, s); 128.1 (*Ph*, s); 128.3 (*Ph*, s); 128.9 (*Ph*, s); 130.8 (*Ph*, s); 138.1 (*Ph*, s); 139.1 (*Ph*, s); **^{31}P** δ 26.4 (*P*H, dm, 1P, $^1J_{PH}$ = 529 Hz); 34.3 (N—CH—*P*, m, 1P).

MS: (−) 535.1 [M−H^+]$^-$. (+) 537.1 [M+H^+]$^+$; 559.2 [M+Na^+]$^+$; 581.4 [M−H^++2Na^+]$^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 5:1): R_f = 0.6.

EA ($C_{26}H_{42}N_4O_4P_2 \cdot 2H_2O$, M_R = 572.6): C 54.5 (54.7); H 8.1 (7.7); N 9.8 (10.0).

Example 6: *Synthesis of compound* ***6***



In a glass flask (50 mL), **5**·2H_2O (103 mg; 180 μmol; 1.0 equiv.) was dissolved in aqueous HCl (1%; 10 mL). Solution of $HgCl_2$ (83.1 mg; 306 μmol; 1.7 equiv.) in H_2O (10 mL) was added and the mixture was stirred at 60 °C overnight. Precipitate was filtered off and the mother liquour was saturated with H_2S. Precipitate was

filtered off, washed with H_2O and the filtrate was evaporated to dryness. The residue was further dried on vaccum pump and subsequently in vaccum dessicator over P_2O_5. Product was obtained as a white substance (106 mg; 84%; 1 step, based on **5**·2H_2O).

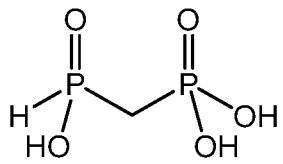
NMR (D_2O): **^{1}H** δ 1.76 (CH_2—CH_2—CH_2, p, 2H, $^3J_{HH}$ = 4 Hz); 1.88 (CH_2—CH_2—CH_2, m, 2H); 2.03 (P—CH_2—P, dd, 2H, $^2J_{HP}$ = 18 Hz, $^2J_{HP}$ = 14 Hz); 2.44 (*cycle*, m, 2H); 2.51–2.63 (*cycle*, m, 4H); 2.69–3.30 (*cycle*, N—CH_2—P, m, 10H); 3.72 (CH_2—Ph, s, 2H); 3.74 (CH_2—Ph, s, 2H); 7.16 (*Ph*, m, 2H); 7.25–7.34 (*Ph*, m, 8H); **^{13}C**{^{1}H} δ 24.9 (CH_2—*C*H_2—CH_2, s); 26.9 (CH_2—*C*H_2—CH_2, s); 36.6 (P—*C*H_2—P, dd, $^1J_{CP}$ = 114 Hz, $^1J_{CP}$ = 70 Hz); 40.8 (*cycle*, s); 42.2 (*cycle*, s); 50.3 (*cycle*, d, $^3J_{CP}$ = 7 Hz); 52.8 (*cycle*, s); 53.5 (*cycle*, s); 53.6 (*cycle*, s); 53.8 (*cycle*, d, $^3J_{CP}$ = 9 Hz); 54.8 (*cycle*, s); 55.3 (*C*H_2—Ph, s); 58.8 (*C*H_2—Ph, s); 60.1 (N—*C*H_2—P, d, $^1J_{CP}$ = 106 Hz); 125.2 (*Ph*, s); 125.9 (*Ph*, s); 128.1 (*Ph*, s); 128.3 (*Ph*, s); 130.0 (*Ph*, s); 130.2 (*Ph*, s); 138.5 (*Ph*, s); 140.3 (*Ph*, s); **^{31}P**{^{1}H} δ 21.4 (HO—*P*—OH, d, 1P, $^2J_{PP}$ = 9 Hz); 33.3 (N—CH—*P*, d, 1P, $^2J_{PP}$ = 9 Hz).

MS: (−) 551.1 $[M-H^+]^-$.

TLC (SiO_2, EtOH–conc. NH_4OH 5:1): R_f = 0.2.

EA ($C_{26}H_{42}N_4O_5P_2$·3.5HCl·H_2O, M_R = 698.2): C 44.7 (45.0); H 6.9 (6.7); N 8.0 (8.1).

Example 7: *Synthesis of intermediate product* ***A***



In a glass flask, methylene-bis(phosphinic acid) (2.50 g; 17.4 mmol; 1.0 equiv.) was dissolved in H_2O (50 mL). Solution of $HgCl_2$ (5.90 g; 21.7 mmol; 1.2 equiv.) in H_2O (50 mL) was added and the mixture was stirred at 60 °C for three days. Precipitate was filtered off, washed with H_2O and the mother liquour was saturated with H_2S. Precipitate was filtered off, washed with H_2O and the filtrate was evaporat to dryness. The crude product was further purified by column chromatography (SiO_2; *i*PrOH–conc. NH_4OH–H_2O 7:3:3; R_f = 0.2). The fractions with product were combined and evaporated to dryness. The residue was suspended in H_2O (25 mL), treated with small amounts of charcoal and filtered through syringe microfilter (Millipore; 0.22 μm). The filtrate was re-purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O). Aqueous fraction with product was evaporated to

dryness and the residue was further dried on vaccum pump and subsequently in vaccum dessicator over P_2O_5. Product was obtained as a white substance (1.24 g; 42%; 1 step, based on methylene-bis(phosphinic acid).

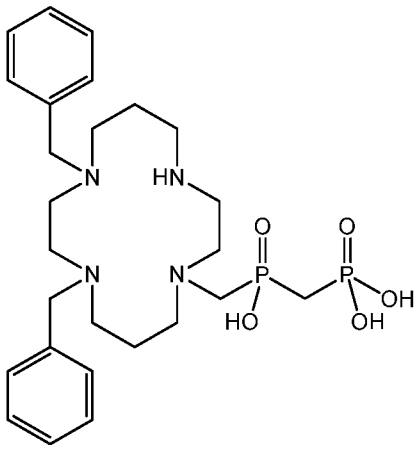
NMR (D_2O): **^{1}H** δ 1.93 (CH_2—P, tm, 2H, $^2J_{HP}$ = 18 Hz); 7.10 (PH, dm, 1H, $^1J_{HP}$ = 526 Hz); **^{13}C**{^{1}H} δ 34.6 (CH$_2$, dd, $^1J_{CP}$ = 114 Hz, $^1J_{CP}$ = 78 Hz); **^{31}P** δ 12.3 (HO—P—OH, td, $^2J_{PH}$ = 18 Hz, $^2J_{PP}$ = 4 Hz); 24.9 (HO—P—H, dtd, $^1J_{PH}$ = 526 Hz, $^2J_{PH}$ = 18 Hz, $^2J_{PP}$ = 4 Hz).

MS: (−) 158.6 $[M-H^+]^-$. (+) 160.8 $[M+H^+]^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 1:1): R_f = 0.2.

EA ($CH_6O_5P_2 \cdot 0.5H_2O$, M_R = 169.0): C 7.1 (7.1); H 4.2 (4.0).

Example 8: *Synthesis of compound 7*



To a glass vial (20 ml), tetrahydrochloride of 1,4-dibenzyl-1,4,8,11-tetraazacyclotetradecane (554 mg; 1.05 μmol; 2.0 equiv.) was added. The intermediate **A**·0.5H_2O (355 mg; 1.05 mmol; 2.0 equiv.). CF_3COOH (5 mL), aqueous HCl (12 M; 5 mL) and paraformaldehyde (23.1 mg; 525 μmol; 1.0 equiv.) were subsequently added and the resulting suspension was stirred at 80 °C for two days. The mixture was evaporated to dryness and several times co-evaporated with H_2O. The crude product was further purified by column chromatography (SiO_2; EtOH–conc. NH_4OH 5:1; R_f = 0.3). The fractions with product were combined and evaporated to dryness. The residue was suspended in H_2O (25 mL), treated with small amounts of charcoal and filtered through syringe microfilter (Millipore; 0.22 μm). The filtrate was re-purified by ion exchange chromatography (DOWEX 50; H^+-form; $H_2O \rightarrow$ 10% aqueous pyridine). The pyridine fraction with product was evaporated to dryness and further co-evaporated several times with H_2O. The residue was re-dissolved in H_2O (100 mL) and subsequently lyophilized.

Product was obtained as a white substance (198 mg; 62%; 1 step, based on paraformaldehyde).

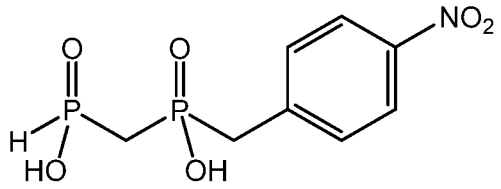
NMR (D_2O): **^{1}H** δ 1.74–1.92 (CH_2—CH_2—CH2, bm, 4H); 2.09 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 16 Hz); 2.44–2.49 *cycle*, bm, 3H); 2.54 (*cycle*, m, 1H); 2.64–2.67 (*cycle*, m, 3H); 2.82–3.16 (*cycle*, N—CH_2—P, bm, 11H); 3.84 (CH_2—Ph, s, 2H); 3.96 (CH_2—Ph, s, 2H); 7.14–7.33 (Ph, bm, 6H); 7.37 (Ph, m, 2H); 7.44 (Ph, m, 2H); **^{13}C**{^{1}H} δ 25.5 (CH_2—CH_2—CH_2, s); 25.9 (CH_2—CH_2—CH_2, s); 36.6 (P—CH_2—P, dd, $^1J_{CP}$ = 118 Hz, $^1J_{CP}$ = 83 Hz); 41.3 (*cycle*, s); 41.4 (*cycle*, s); 48.9 (*cycle*, s); 49.7 (*cycle*, d, $^3J_{CP}$ = 10 Hz); 52.4 (*cycle*, s); 54.6 (*cycle*, s); 55.5 (*cycle*, d, $^3J_{CP}$ = 10 Hz); 55.8 (*cycle*, s); 59.8 (CH_2—Ph, s); 60.1 (N—CH_2—P, d, $^1J_{CP}$ = 109 Hz); 61.3 (CH_2—Ph, s); 126.0 (*Ph*, s); 127.4 (*Ph*, s); 130.2 (*Ph*, s); 130.7 (*Ph*, s); 131.4 (*Ph*, s); 132.2 (*Ph*, s); 134.2 (*Ph*, s); 137.6 (*Ph*, s); **^{31}P**{^{1}H} δ 19.2 (HO—*P*—OH, d, 1P, $^2J_{PP}$ = 7 Hz); 36.2 (N—CH—*P*, d, 1P, $^2J_{PP}$ = 7 Hz).

MS: (−) 535.4 $[M-H^+]^-$. (+) 537.3 $[M+H^+]^+$; 559.5 $[M+Na^+]^+$; 581.2 $[M-H^++2Na^+]^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 5:1): R_f = 0.3.

EA ($C_{26}H_{42}N_4O_4P_2 \cdot 4H_2O$, M_R = 608.6): C 50.9 (51.3); H 8.0 (8.3); N 9.4 (9.2).

Example 9: *Synthesis of intermediate product* ***B***



In a glass flask (100 mL), methylene-bis(phosphinic acid) (1.04 g; 7.22 mol; 1.0 equiv.) was suspended in dry CH_2Cl_2 (25 mL). *N,N*-diisopropylethylamine (9.90 mL; 57.8 mmol; 8.0 equiv.) was added and the flask was washed by gentle stream of argon gas. Then trimethylsilylchloride was added (5.50 mL; 43.5 mmol; 6.0 equiv.) and the resulting mixture was stirred at room temperature for one hour. Solution of 4-nitrobenzylbromidu (1.87 g; 8.66 mmol; 1.2 equiv.) in dry CH_2Cl_2 (20 mL) was added and the resulting mixture was stirred at room temperature for three days. Reaction was stopped by addition of EtOH (25 mL). The mixture was evaporated to dryness and further co-evaporated several times with EtOH. The residue was suspended in H_2O (100 mL). The solid material was filtered off and the filtrate was evaporated to dryness. Crude product was purified by ion exchange chromatography (DOWEX 1; OH^--form; H_2O → 50% AcOH → 3% HCl). The latter fraction was evaporated to

dryness and further purified by ion exchange chromatography (Amberlite CG50; H^+-form; H_2O). Fraction with pure product were combined and evaporated to dryness and the residue was further dried on vaccum pump and subsequently in vaccum dessicator over P_2O_5. Product was obtained as a yellow substance (1.40 g; 69%; 1 step, based on methylene-bis(phosphinic acid).

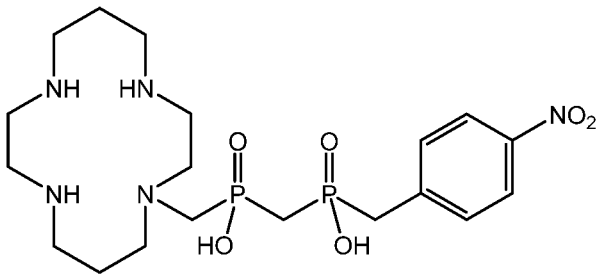
NMR (D_2O): **^{1}H** δ 2.28 (P—C*H*$_2$—P, m, 2H); 3.29 (C*H*$_2$—C, d, 2H, $^2J_{HP}$ = 17 Hz); 7.16 (P*H*, d, 1H, $^1J_{HP}$ = 532 Hz); 7.53 (C*H*—C—CH$_2$, d, 2H, $^2J_{HH}$ = 9 Hz); 8.21 (C*H*—C—N, d, 2H, $^2J_{HH}$ = 9 Hz); **^{13}C**{^{1}H} δ 35.3 (P—*C*H$_2$—P, t, $^1J_{CP}$ = 78 Hz); 40.4 (P—*C*H$_2$—C, d, $^1J_{CP}$ = 86 Hz); 124.3 (*C*H—C—N, s); 131.3 (*C*H—C—CH$_2$, d, $^3J_{CP}$ = 4 Hz); 144.0 (CH—*C*—CH$_2$, d, $^2J_{CP}$ = 8 Hz); 146.7 (CH—*C*—N, s); **^{31}P** δ 18.7 (*P*H, dt, 1P, $^1J_{PH}$ = 532 Hz; $^2J_{PH}$ = 18 Hz); 30.5 (CH$_2$—*P*—CH$_2$, p, 1P, $^2J_{PH}$ = 17 Hz).

MS: (−) 277.5 [M−H$^+$]$^-$.

TLC (SiO_2, EtOH–conc. NH_4OH 5:1): R_f = 0.5.

EA ($C_8H_{11}NO_6P_2$, M_R = 279.1): C 34.4 (34.2); H 4.0 (3.9); N 5.0 (4.8).

Example 10: *Synthesis of compound* ***8***



To a glass flask (100 ml), 1,4,8,11-tetraazacyklotetradecane (3.38 g; 16.9 mmol; 3.6 equiv.) was added. Intermediate **B** (1.31 g; 4.69 mmol; 1.0 equiv.), paraformaldehyde (169 mg; 5.63 mmol; 1.2 equiv.) and aqueous HCl (6 M; 60 mL) were subsequently added and the resulting mixture was stirred at 80 °C overnight. The mixture was evaporated to dryness and co-evaporated several times with H_2O. The crude product was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O → 10% aqueous pyridine). Pyridine fraction with product was evaporated to dryness and several times co-evaporated with H_2O. The residue was purified by ion exchange chromatography (DOWEX 1; OH^--form; H_2O → 10% aqueous AcOH). Acetate fraction with product was evaporated to dryness and several times co-evaporated with H_2O. The residue was further dried on vaccum pump and

subsequently in vaccum dessicator over P_2O_5. Product was obtained as a white substance (1.67 g; 71%; 1 step, based on intermediate **B**).

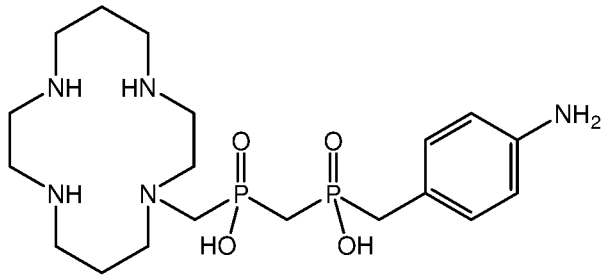
NMR (D_2O): **^{1}H** δ 1.70 (CH_2—CH_2—CH_2, p, 2H, $^3J_{HH}$ = 5 Hz); 1.76 (CH_2—CH_2—CH_2, p, 2H, $^3J_{HH}$ = 5 Hz); 2.01 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 16 Hz); 2.55–2.83 (*cycle*, N—CH_2—P, m, 18H); 3.32 (CH_2—C—CH, d, 2H, $^2J_{HP}$ = 17 Hz); 7.56 (C*H*—C—CH_2, d, 2H, $^2J_{HH}$ = 9 Hz); 8.21 (C*H*—C—N, d, 2H, $^2J_{HH}$ = 9 Hz); **^{13}C**{^{1}H} δ 25.4 (CH_2—*C*H_2—CH_2, s); 27.0 (CH_2—*C*H_2—CH_2, s); 33.2 (P—*C*H_2—P, t, $^1J_{CP}$ = 79 Hz); 40.8 (P—*C*H_2—C, d, $^1J_{CP}$ = 86 Hz); 46.0 (*cycle*, s); 46.2 (*cycle*, s); 46.7 (*cycle*, s); 46.8 (*cycle*, s); 47.9 (*cycle*, s); 48.9 (*cycle*, s); 54.8 (*cycle*, s); 54.5 (*cycle*, s); 55.2 (P—*C*H_2—N, d, $^1J_{CP}$ = 110 Hz); 124.3 (*C*H—C—N, s); 131.3 (*C*H—C—CH_2, d, $^3J_{CP}$ = 4 Hz); 144.6 (CH—*C*—CH_2, s); 146.6 (CH—*C*—N, s); **^{31}P**{^{1}H} δ 31.6 (CH_2—*P*—CH_2, d, 1P, $^2J_{PP}$ = 9 Hz); 32.9 (CH_2—*P*—CH_2, d, 1P, $^2J_{PP}$ = 9 Hz).

MS: (−) 489.7 $[M-H^+]^-$. (+) 491.9 $[M+H^+]^+$; 513.9 $[M+Na^+]^+$; 529.8 $[M+K^+]^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 1:1): R_f = 0.7.

EA ($C_{19}H_{35}N_5O_6P_2 \cdot 0.5H_2O$, M_R = 500.5): C 45.6 (45.2); H 7.3 (7.6); N 14.0 (13.8).

Example 11: *Synthesis of compound* ***9***



In a glass flask (100 ml), **8**·0.5H_2O (512 mg; 1.02 mmol; 1.0 equiv.) was dissolved in H_2O and the resulting mixture was briefly washed with gaseous argon. Ammonium formate (1.98 g; 31.4 mmol; 31 equiv.) and Pd@C catalyst (10%; 54 mg) were subsequently added. Resulting suspension was stirred at 60 °C for three hours. Another portion of ammonium formate (658 mg; 10.4 mmol; 10 equiv.) and Pd@C catalyst (10%; 52 mg) was added and the mixture was further stirred at 60 °C for two days. The mixture was then evaporated to dryness and several times evaporated with H_2O. The residue was dissolved in H_2O, catalyst was filtered off and the filtrate was purified by ion exchange chromatography (DOWEX 1; OH^--forma; $H_2O \rightarrow$ 10% aqueous AcOH). Acetate fraction with product was evaporated to dryness and then several times co-evaporated with H_2O. The residue was purified by ion exchange

chromatography (DOWEX 50; H^+-forma; $H_2O \rightarrow$ 10% aqueous pyridine). Pyridine fraction with product was evaporated to dryness and further co-evaporated several times with H_2O. The residue was re-dissolved in H_2O (150 ml) and lyophilized. Product was obtained as an off-white substance (443 mg; 84%; 1 step; based on **8**·0.5H_2O).

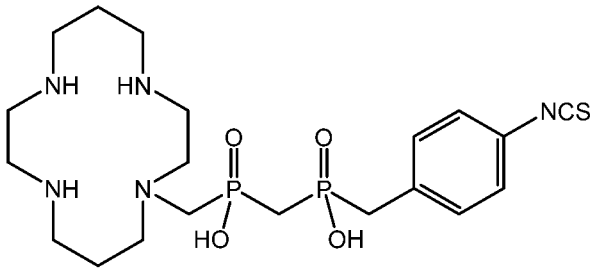
NMR (D_2O): **^{1}H** δ 1.72 (CH_2—CH_2—CH_2, p, 2H, $^3J_{HH}$ = 5 Hz); 1.79 (CH_2—CH_2—CH_2, p, 2H, $^3J_{HH}$ = 5 Hz); 1.96 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 15 Hz); 2.62–2.88 (*cycle*, N—CH_2—P, m, 18H); 3.02 (CH_2—C—CH, d, 2H, $^2J_{HP}$ = 17 Hz); 6.82 (CH—C—CH_2, d, 2H, $^2J_{HH}$ = 8 Hz); 7.18 (CH—C—N, d, 2H, $^2J_{HH}$ = 8 Hz); **^{13}C**{^{1}H} 25.0 (CH_2—CH_2—CH_2, s); 26.7 (CH_2—CH_2—CH_2, s); 32.7 (P—CH_2—P, t, $^1J_{CP}$ = 78 Hz); 39.4 (P—CH_2—C, d, $^1J_{CP}$ = 91 Hz); 45.7 (*cycle*, s); 46.2 (*cycle*, s); 46.7 (*cycle*, s); 46.8 (*cycle*, s); 48.7 (*cycle*, s); 49.4 (*cycle*, s); 54.8 (*cycle*, s); 54.9 (*cycle*, s); 55.0 (P—CH_2—N, d, $^1J_{CP}$ = 109 Hz); 117.3 (CH—C—N, s); 126.4 (CH—C—CH_2, d, $^3J_{CP}$ = 8 Hz); 131.4 (CH—C—CH_2, s); 144.8 (CH—C—N, s); **^{31}P**{^{1}H} δ 33.7 (CH_2—P—CH_2, d, 1P, $^2J_{PP}$ = 9 Hz); 34.6 (CH_2—P—CH_2, d, 1P, $^2J_{PP}$ = 9 Hz).

MS: (−) 459.8 $[M-H^+]^-$. (+) 461.9 $[M+H^+]^+$; 483.9 $[M+Na^+]^+$; 499.9 $[M+K^+]^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 1:1): R_f = 0.6.

EA ($C_{19}H_{37}N_5O_4P_2$·3H_2O, M_R = 515.5): C 44.3 (44.4); H 8.4 (8.6); N 13.6 (13.6).

Example 12: *Synthesis of compound* ***10***



In a glass vial (20 mL), **9**·3H_2O (53.4 mg; 104 μmol; 1.0 equiv.) was dissolved in H_2O. The solution was acidified by aqueous HCl (1.12 M; 185 μL; 207 μmol; 2.0 equiv.). Freshly prepared solution of $CSCl_2$ (16 μL; 209 μmol; 2.0 equiv.) in CCl_4 (5 mL) was then added and the resulting biphasic mixture was vigorously stirred at room temperature overnight. Organic layer was separated and the aqueous layer was extracted with CCl_4 (2×20 mL) and Et_2O (1×20 mL). Aqueous layer was then separated and evaporated to dryness. The crude product was purified by preparative HPLC (C8; gradient elution H_2O–0,1% TFA–MeCN). Fraction with product was

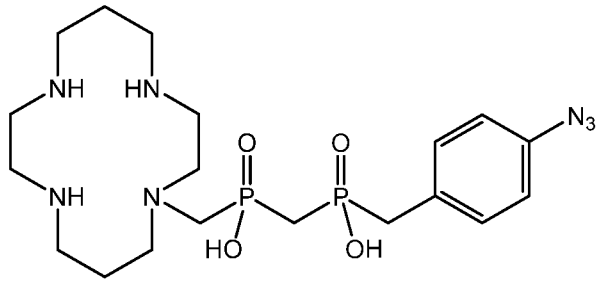
directly lyophilized. Product was obtained as a white substance (70.9 mg; 79%; 1 step; based on **9**·3H_2O).

NMR (D_2O): **^{1}H** δ 2.19 (CH_2—CH_2—CH_2, m, 4H); 2.40 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 16 Hz); 3.13–3.60 (*cycle*, N—CH_2—P, P—CH_2—C, m, 20H); 7.36 (C*H*, m, 4H); **^{13}C**{^{1}H} δ 21.1 (CH_2—*C*H_2—CH_2, s); 21.7 (CH_2—*C*H_2—CH_2, s); 32.8 (P—*C*H_2—P, t, $^1J_{CP}$ = 81 Hz); 38.8 (P—*C*H_2—C, d, $^1J_{CP}$ = 91 Hz); 40.5 (*cycle*, s); 41.4 (*cycle*, s); 42.8 (*cycle*, s); 43.1 (*cycle*, s); 43.9 (*cycle*, s); 44.3 (*cycle*, s); 52.9 (*cycle*, s); 54.3 (P—*C*H_2—N, d, $^1J_{CP}$ = 100 Hz); 54.4 (*cycle*, s); 126.7 (*C*H—C—N, s); 130.1 (CH—*C*—N, s); 131.6 (*C*H—C—CH_2, d, $^3J_{CP}$ = 5 Hz); 132.9 (CH—*C*—CH_2, d, $^2J_{CP}$ = 8 Hz); 134.8 (N*C*S, s); **^{31}P**{^{1}H} δ 27.0 (CH_2—*P*—CH_2, bm, 1P); 39.1 (CH_2—*P*—CH_2, d, 1P, $^2J_{PP}$ = 7 Hz).

MS: (−) 501.8 [M−H$^+$]$^-$. (+) 504.0 [M+H$^+$]$^+$.

EA ($C_{20}H_{35}N_5O_4P_2S$·TFA·3.5H_2O, M_R = 863.3): C 30.6 (30.8); H 5.0 (4.8); N 8.1 (8.0).

Example 13: *Synthesis of compound* ***11***



In a glass vial (4 mL), **9**·3H_2O (40.2 mg; 78.0 μmol; 1.3 equiv.) was dissolved in aqueous HCl (243.8 mM; 962 μL; 235 μmol; 4.0 equiv.) and the resulting mixture was cooled in an ice bath (1 °C). Freshly prepared aqueous solution of $NaNO_2$ was then gradually added (290 mM; 200 μL; 58.0 μmol; 1.0 equiv.; 20 μL each three minutes). Freshly prepared aqueous solution of NaN_3 (580 mM; 200 μL; 116 μmol; 2.0 equiv.) was then added. The reaction mixture was then stirred at room temperature for three hours. The crude product was purified by preparative HPLC (C8; gradient elution H_2O–0,1% TFA–MeCN). Fraction with product was directly lyophilized. Product was obtained as a white substance (29.5 mg; 57%; 1 step; based on **9**·3H_2O).

NMR (D_2O): **^{1}H** δ 2.07 (CH_2—CH_2—CH_2, p, 2H, $^3J_{HH}$ = 6 Hz); 2.13 (CH_2—CH_2—CH_2, p, 2H, $^3J_{HH}$ = 7 Hz); 2.20 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 16 Hz); 2.80–3.57 (*cycle*, N—CH_2—P, P—CH_2—C, bm, 20H); 7.11 (C*H*—C—N, d, 2H, $^3J_{HH}$ = 8 Hz); 7.34

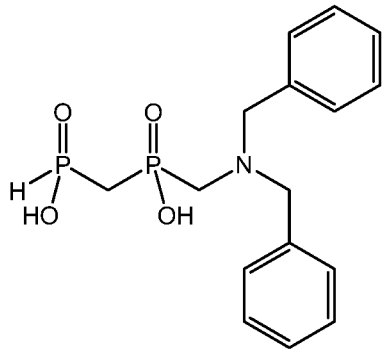
(C*H*—C—CH_2, d, 2H, $^3J_{HH}$ = 8 Hz); $^{13}C\{^1H\}$ δ 22.4 (CH_2—*C*H_2—CH_2, s); 22.7 (CH_2—*C*H_2—CH_2, s); 32.3 (P—*C*H_2—P, t, $^1J_{CP}$ = 80 Hz); 39.3 (P—*C*H_2—C, d, $^1J_{CP}$ = 91 Hz); 42.4 (*cycle*, s); 43.5 (*cycle*, s); 44.3 (*cycle*, s); 45.1 (*cycle*, s); 45.4 (*cycle*, s); 46.0 (*cycle*, s); 53.7 (P—*C*H_2—N, d, $^1J_{CP}$ = 105 Hz); 54.6 (*cycle*, s); 55.6 (*cycle*, s); 119.9 (*C*H—C—N, s); 130.9 (CH—*C*—CH_2, d, $^2J_{CP}$ = 8 Hz); 131.8 (*C*H—C—CH_2, d, $^3J_{CP}$ = 5 Hz); 139.0 (CH—*C*—N, s); $^{31}P\{^1H\}$ δ 29.6 (CH_2—*P*—CH_2, bm, 1P); 37.1 (CH_2—*P*—CH_2, d, 1P, $^2J_{PP}$ = 9 Hz).

MS: (−) 485.8 $[M-H^+]^-$. (+) 488.0 $[M+H^+]^+$; 509.9 $[M+Na^+]^+$; 531.9 $[M+K^+]^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 2:1): R_f = 0.7.

EA ($C_{19}H_{35}N_7O_4P_2 \cdot 0.5TFA \cdot 1.5H_2O$, M_R = 662.9): C 36.2 (36.4); H 5.9 (5.6); N 14.8 (15.0).

Example 14: *Synthesis of intermediate product* ***C***



In a glass flask (100 mL), methylene-bis(phosphinic acid) (2.32 g; 16.1 mol; 1.0 equiv.) and dibenzylamine (4.03 mL; 21.0 mmol; 1.3 equiv.) were suspended in a mixture of 6 M aqueous HCl–THF (1:1; 50 mL). Paraformaldehyde (726 mg; 24.2 mmol; 1.5 equiv.) was then added, the flask was quickly sealed with stopper and the resulting mixture was stirred at 80 °C overnight. After cooling to room temperature, the mixture was evaporated to dryness. The residue was dissolved in H_2O and washed with CH_2Cl_2. Aqueous layer was separated, evaporated to dryness and the residue was purified was purified by flash chromatography (C18; gradient elution H_2O–0,1% TFA–MeCN). Fraction with product was evaporated to dryness and the residue was re-dissolved in small volume of MeOH. Et_2O was subsequently added until cloudiness. Next day, the formed precipitate was collected on glass frit S3 and washed with Et_2O. Product was obtained as a white substance (2.27 mg; 37%; 1 step; based on methylene-bis(phosphinic acid)).

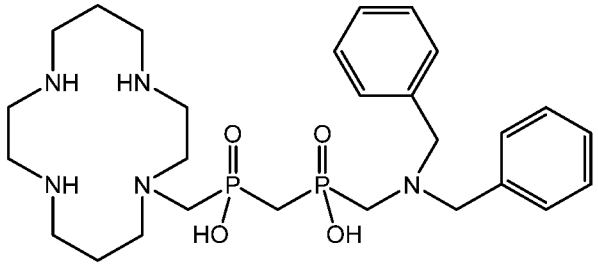
NMR (D_2O): **^{1}H** δ 2.02 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 17 Hz); 3.25 (P—CH_2—N, d, 2H, $^2J_{HP}$ = 11 Hz); 4.46 (CH_2—Ph, m, 4H); 7.15 (P*H*, d, 1H, $^1J_{HP}$ = 562 Hz); 7.52 (*Ph*, m, 10H); **^{13}C**{^{1}H} δ 35.8 (P—*C*H_2—P, t, $^1J_{CP}$ = 81 Hz); 51.7 (P—*C*H_2—N, d, $^1J_{CP}$ = 92 Hz); 59.4 (*C*H_2—Ph, s); 129.8 (*C*—CH_2, s); 129.9 (*Ph*, s); 130.8 (*Ph*, s); 132.1 (*Ph*, s); **^{31}P** δ 20.9 (*P*—CH_2—N, m, 1P); 22.1 (*P*H, dm, 1P, $^1J_{PH}$ = 562 Hz).

MS: (−) 351.6 [M−H$^+$]$^-$. (+) 353.7 [M+H$^+$]$^+$; 391.7 [M+K$^+$]$^+$.

TLC (SiO_2, MeOH): R_f = 0.6.

EA ($C_{16}H_{21}NO_4P_2$·MeOH, M_R = 385.3): C 53.0 (53.1); H 6.5 (6.2); N 3.6 (3.9).

Example 15: *Synthesis of compound* ***12***



To a glass flask (100 ml), 1,4,8,11-tetraazacyklotetradecane (3.26 g; 16.3 mmol; 5.5 equiv.) was added. Intermediate **C**·MeOH (1.15 g; 2.99 mmol; 1.0 equiv.), paraformaldehyde (160 mg; 5.33 mmol; 1.8 equiv.) and aqueous HCl (6 M; 60 mL) were subsequently added and the resulting mixture was stirred at 80 °C overnight. Mixture was evaporated to dryness and co-evaporated several times with H_2O. Crude product was purified by ion exchange chromatography (DOWEX 50; H$^+$-form; H_2O → 5% aqueous ammonia). Ammonia fraction with product was evaporated to dryness and several times co-evaporated with H_2O. The residue was purified by ion exchange chromatography (DOWEX 1; OH$^-$-form; H_2O → 10% aqueous AcOH). Acetate fraction with product was evaporated to dryness and several times co-evaporated with H_2O. The residue was further dried on vaccum pump and subsequently in vaccum dessicator over P_2O_5. Product was obtained as a white substance (1.46 g; 74%; 1 step, based on intermediate **C**·MeOH).

NMR (D_2O): **^{1}H** δ 1.67 (CH_2—CH_2—CH_2, p, 2H, $^3J_{HH}$ = 5 Hz); 1.71 (CH_2—CH_2—CH_2, p, 2H, $^3J_{HH}$ = 5 Hz); 2.07 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 15 Hz); 2.55–2.73 (N—CH_2—P, *cycle*, m, 18H); 2.76 (N—CH_2—P, d, 2H, $^2J_{HP}$ = 9 Hz); 3.79 (CH_2—Ph, s, 4H); 7.32–7.49 (*Ph*, m, 10H); **^{13}C**{^{1}H} δ 25.1 (CH_2—*C*H_2—CH_2, s); 27.0 (CH_2—*C*H_2—CH_2, s); 33.5 (P—*C*H_2—P, t, $^1J_{CP}$ = 77 Hz); 45.7 (*cycle*, s); 45.9 (*cycle*, s); 46.3

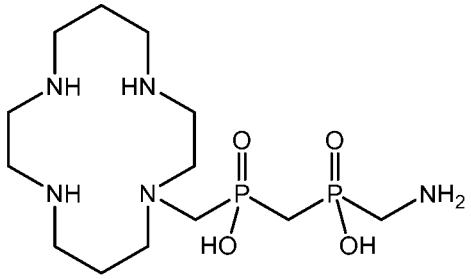
(*cycle*, s); 46.4 (*cycle*, s); 53.7 (*cycle*, s); 54.6 (*cycle*, s); 54.9 (P—*C*H_2—N, d, $^1J_{CP}$ = 107 Hz); 55.2 (P—*C*H_2—N, d, $^1J_{CP}$ = 109 Hz); 58.9 (*C*H_2—Ph, d, $^3J_{CP}$ = 6 Hz); 127.8 (*Ph*, s); 128.9 (*Ph*, s); 130.3 (*Ph*, s); 139.0 (*Ph*, s); ^{31}**P**{^{1}H} δ 33.1 (*P*—CH_2—N, d, 1P, $^2J_{PP}$ = 12 Hz) 33.6 (*P*—CH_2—N, d, 1P, $^2J_{PP}$ = 12 Hz).

MS: (−) 563.8 $[M-H^+]^-$. (+) 566.0 $[M+H^+]^+$; 588.0 $[M+Na^+]^+$; 604.0 $[M+K^+]^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 2:1): R_f = 0.8.

EA ($C_{27}H_{45}N_5O_4P_2$·AcOH·1.5H_2O, M_R = 657.2): C 53.4 (53.4); H 8.0 (7.7); N 10.7 (10.6).

Example 16: *Synthesis of compound* ***13***



In a glass flask (250 mL), **12**·AcOH·1.5H_2O (1.55 g; 2.36 mmol) was dissolved in H_2O and the resulting solution was briefly washed with argon gas. $HCOONH_4$ (4.45 g; 70.5 mmol; 30 equiv.) and catalyst (10% Pd@C; 113 mg) were subsequently added and the resulting suspension was stirred at 60 °C for three hours. Another portion of $HCOONH_4$ (1.48 g; 23.5 mmol; 10 equiv.) and catalyst (10% Pd@C; 41 mg) was added and the mixture was further stirred for two days. The mixture was evaporated to dryness and further co-evaporated several times with H_2O. The residue was dissolved in H_2O, catalyst was filtered off and the filtrate was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O → 5% aqueous ammonia). Ammonia fraction with product was evaporated to dryness and further co-evaporated several times with H_2O. The residue was re-dissolved in H_2O (150 ml) and lyophilized. Product was obtained as an off-white substance (720 mg; 74%; 1 step; based on **13**·AcOH·1.5H_2O).

NMR (D_2O): ^{1}**H** δ 1.69 (CH_2—C*H*$_2$—CH_2, p, 2H, $^3J_{HH}$ = 6 Hz); 1.81 (CH_2—C*H*$_2$—CH_2, m, 2H); 2.11 (P—C*H*$_2$—P, dd, 2H, $^2J_{HP}$ = 17 Hz, $^2J_{HP}$ =15 Hz); 2.61–3.32 (N—C*H*$_2$—P, *cycle*, m, 20H); ^{13}**C**{^{1}H} δ 29.2 (CH_2—*C*H_2—CH_2, s); 30.1 (CH_2—*C*H_2—CH_2, s); 36.4 (P—*C*H_2—P, t, $^1J_{CP}$ = 78 Hz); 39.9 (*cycle*, s); 42.2 (*cycle*, s); 43.3 (*cycle*, s); 44.3 (*cycle*, s); 45.8 (*cycle*, s); 51.1 (*cycle*, s); 51.8 (P—*C*H_2—N, d, $^1J_{CP}$ =

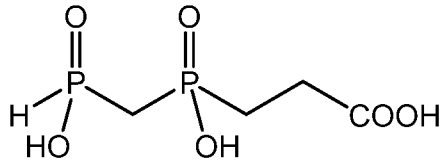
105 Hz); 57.8 (P—CH_2—N, d, $^1J_{CP}$ = 102 Hz); ^{31}**P**{^{1}H} δ 24.0 (*P*—CH_2—NH_2, d, 1P, $^2J_{PP}$ = 5 Hz); 31.3 (C—N—CH_2— *P*, d, 1P, $^2J_{PP}$ = 5 Hz).

MS: (−) 383.9 $[M-H^+]^-$. (+) 385.7 $[M+H^+]^+$; 407.9 $[M+Na^+]^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 1:1): R_f = 0.6.

EA ($C_{13}H_{33}N_5O_4P_2 \cdot 2.5H_2O$, M_R = 412.4): C 40.5 (40.3); H 8.6 (8.9); N 18.2 (18.4).

Example 17: *Synthesis of intermediate* ***D***



In a argon-washed three-necked flask (1000 mL), methylene-bis(phosphinic acid) (2.50 g; 17.4 mol; 1.0 equiv.) was suspended in hexamethyldisilizane (150 mL; 716 mmol; 41 equiv.) and the resulting mixture was stirred at 110 °C under gentle flow of argon overnight. The mixture was then cooled to room temperature and dry CH_2Cl_2 (100 mL) was subsequenty added followed by addition of *tert*-butyl acrylate (5.00 mL; 34.2 mmol; 2.0 equiv.) in dry CH_2Cl_2 (100 mL). The resulting mixture was further stirred at room temperature overnight. Reaction was quenched with EtOH (150 mL) and the resulting mixture was evaporated to dryness. The crude product was purified by flash chromatography (C18; gradient elution H_2O–0,1% TFA–MeCN). Fractions with pure product were combined and evaporated to dryness. The residue was further purified by ion exchange chromatography (Amberlite CG50; H^+-form; H_2O). Aqueous fraction was evaporated to dryness and further co-evaporated several times with CH_2Cl_2. Residue was dissolved in CH_2Cl_2–TFA (1:1; 200 mL) and the resulting mixture was stirred overnight at RT in the absence of light. Reaction mixture was then evaporated to dryness and the residue was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O). Fractions with product were combined and evaporated to dryness. The residue was further purified on vacuum pump and subsequently in vacuum dessicator over P_2O_5. Product was obtained as a white substance (1.41 g; 38%; 2 steps; based on methylene-bis(phosphinic acid)).

NMR (D_2O): ^{1}**H** δ 1.97 (P—C*H*$_2$—CH_2, m, 2H); 2.21 (P—C*H*$_2$—P, t, 2H, $^2J_{HP}$ = 17 Hz); 2.46 (P—CH_2—C*H*$_2$, m, 2H); 7.01 (P*H*, 1H, d, $^1J_{HP}$ = 560 Hz); ^{13}**C**{^{1}H} 26.2 (P—*C*H$_2$—CH_2, d, $^1J_{CP}$ = 98 Hz); 27.1 (P—CH_2—*C*H$_2$, s); 33.0 (P—*C*H$_2$—P, t, $^1J_{CP}$ =

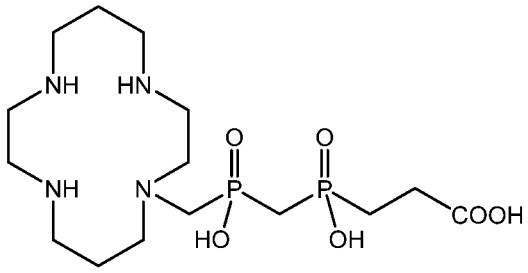
79 Hz); 177.2 (*C*O, d, $^{3}J_{CP}$ = 16 Hz); **^{31}P** δ 19.2 (*P*H, d, 1P, $^{1}J_{PH}$ = 544 Hz); 44.5 (*P*—CH_2—CH_2, m, 1P).

MS: (−) 196.6 $[M-H_3O^+]^-$; 214.5 $[M-H^+]^-$. (+) 216.7 $[M+H^+]^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 1:1): R_f = 0.6.

EA ($C_4H_{10}O_6P_2$, M_R = 216.1): C 22.2 (21.9); H 4.7 (5.0).

Example 18: *Synthesis of compound* ***14***



To a glass vial (20 ml), 1,4,8,11-tetraazacyklotetradecane (1.19 g; 5.95 mmol; 3.8 equiv.) was added. Intermediate **D** (340 mg; 1.57 mmol; 1,0 equiv.), paraformaldehyde (58 mg; 1.3 mmol; 1.2 equiv.) and aqueous HCl (6 M; 10 mL) were subsequently added and the resulting mixture was stirred at 60 °C overnight. Next day, mixture was evaporated to dryness and co-evaporated several times with H_2O. Crude product was purified by ion exchange chromatography (IRA 402; OH^--form; H_2O → 10% aqueous AcOH). Acetate fraction with product was evaporated to dryness and several times co-evaporated with H_2O. The residue was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O → 10% aqueous pyridine). Pyridine fraction with product was evaporated to dryness and several times co-evaporated with H_2O. The residue was re-dissolved in H_2O (50 mL) and subsequently lyophilized. Product was obtained as a white substance (459 mg; 61%; 1 step, based on intermediate **D**).

NMR (D_2O): **^{1}H** δ 1.71 (CH_2—C*H*$_2$—CH_2, p, 2H, $^{3}J_{HH}$ = 5 Hz); 1.76 (CH_2—C*H*$_2$—CH_2, p, 2H, $^{3}J_{HH}$ = 5 Hz); 1.91 (P—C*H*$_2$—C, m, 2H); 2.05 (P—C*H*$_2$—P, t, 2H, $^{2}J_{HP}$ = 16 Hz); 2.37 (C*H*$_2$—CO, m, 2H); 2.65 (*cycle*, t, 2H, $^{3}J_{HH}$ = 5 Hz); 2.69–2.79 (*cycle*, N—C*H*$_2$—P, m, 16H); **^{13}C**{^{1}H} δ 25.6 (CH_2—*C*H$_2$—CH_2, s); 27.2 (CH_2—*C*H$_2$—CH_2, s); 29.7 (P—*C*H$_2$—C, d, $^{1}J_{CP}$ = 96 Hz); 31.2 (*C*H$_2$—CO, s); 33.5 (P—*C*H$_2$—P, t, $^{1}J_{CP}$ = 77 Hz); 46.2 (*cycle*, s); 46.3 (*cycle*, s); 46.8 (*cycle*, s); 46.9 (*cycle*, s); 47.6 (*cycle*, s); 48.8 (*cycle*, s); 54.4 (*cycle*, s); 54.8 (*cycle*, s); 55.2 (N—*C*H$_2$—P, d, $^{1}J_{CP}$ = 109

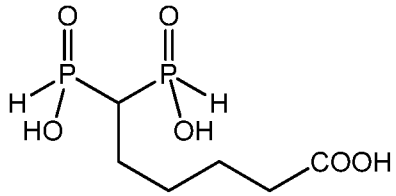
Hz); 183.2 (*C*O, d, $^{3}J_{CP}$ = 19 Hz); ^{31}**P**{^{1}H} δ 33.4 (*P*—CH_2—N, d, 1P, $^{2}J_{PP}$ = 10 Hz); 36.6 (*P*—CH_2—CH_2, d, 1P, $^{2}J_{PP}$ = 10 Hz).

MS: (−) 402.8 $[M-H_3O^+]^-$; 426.7 $[M-H^+]^-$. (+) 428.9 $[M+H^+]^+$; 450.8 $[M+Na^+]^+$; 466.8 $[M+K^+]^+$.

TLC (SiO_2, *i*PrOH–conc.NH_4OH–H_2O 7:1:1): R_f = 0.5.

EA ($C_{15}H_{34}N_4O_6P_2 \cdot 4H_2O$, M_R = 500.5): C 36.0 (36.0); H 8.5 (8.8); N 11.2 (11.2).

Example 19: *Synthesis of intermediate product* ***E***



In a glass beaker (1000 mL), $NaH_2PO_2 \cdot H_2O$ (28.6 g; 270 mmol; 6.0 equiv.) was dissolved in a mixture of MeOH (500 mL) and unstabilized dioxane (75 mL). 5-hexynoic acid (5.00 mL; 45.3 mmol; 1.0 equiv.) and solution of Et_3B in hexanes (1.0 M; 45 mL; 45.0 mmol; 1.0 equiv.) were subsequently added and the resulting mixture was vigorously stirred in presence of air for four hours. The resulting precipitate was collected on glass frit S3 and several times washed with cold MeOH and air dried. The crude product was purified by column chromatography (SiO_2; EtOH–conc. NH_4OH 2:1; R_f = 0.4). Fractions with product were combined and evaporated to dryness. The residue was re-dissolved in H_2O (150 mL) and treated with charcoal. The resulting suspension was filterred through syringe microfilter (Millipore; 0.22 μm) and the filtrate was further purified by ion exchange resin (DOWEX 50; H^+-form; H_2O). Aqueous fraction was evaporated to dryness, re-dissolved in H_2O and subsequently lyophilized (4.31 g; 32%; 1 step; based on Et_3B).

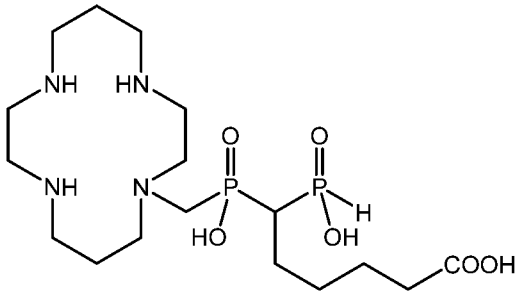
NMR (D_2O): ^{1}**H** δ 1.57 (C*H*$_2$, m, 2H); 1.64 (C*H*$_2$, m, 2H); 1.74 (C*H*$_2$, m, 2H); 1.87 (P—C*H*—P, m, 1H); 2.38 (C*H*$_2$—CO, t, 2H, $^{3}J_{HH}$ = 8 Hz); 7.04 (P*H*, dm, 2H, $^{1}J_{HP}$ = 526 Hz); ^{13}**C**{^{1}H} δ 21.7 (P—CH—CH_2—*C*H$_2$, t, $^{3}J_{CP}$ = 3 Hz); 25.6 (CH_2—*C*H$_2$—CO, s); 29.4 (P—CH—*C*H$_2$, t, $^{2}J_{CP}$ = 7 Hz); 35.2 (*C*H$_2$—CO, s); 44.8 (P—*C*H—P, t, $^{1}J_{CP}$ = 78 Hz); 180.9 (*C*O, s); ^{31}**P** δ 25.8 (dm, $^{1}J_{PH}$ = 526 Hz).

MS: (−) 242.5 $[M-H^+]^-$; 264.5 $[M-2H^+ + Na^+]^-$; 286.5 $[M-3H^+ + 2Na^+]^-$. (+) 310.8 $[M-2H^+ + 3Na^+]^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 2:1): R_f = 0.4.

EA ($C_6H_{14}O_6P_2 \cdot 3H_2O$, M_R = 298.2): C 24.2 (24.1); H 6.8 (6.5).

Example 20: *Synthesis of compound* ***15***



To a glass vial (20 ml), 1,4,8,11-tetraazacyklotetradecane (1.50 g; 7.50 mmol; 3.8 equiv.) was added. Intermediate **E**·$3H_2O$ (1.51 g; 5.08 mmol; 2.6 equiv.), paraformaldehyde (59.2 mg; 1.97 mmol; 1.0 equiv.) and aqueous HCl (6 M; 10 mL) were subsequently added and the resulting mixture was stirred at 70 °C overnight. Next day, the mixture was evaporated to dryness and co-evaporated several times with H_2O. The crude product was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O → 10% aqueous pyridine). Pyridine fraction with product was evaporated to dryness and several times co-evaporated with H_2O. The crude producted was purified by column chromatography (SiO_2; *i*PrOH–konc. NH_4OH–H_2O 7:3:3; R_f = 0.5) Fractions with product were combined and evaporated to dryness. The residue was suspended in H_2O (50 mL) and treated with charcoal. Suspension was then filtered throught syringe microfilter (Millipore; 0.22 μm). The filtrate was re-purified by ion exchange chromatography (IRA 402; OH^--form; H_2O → 10% aqueous AcOH). Acetate fraction with product was evaporated to dryness and several times co-evaporated with H_2O. The residue was re-dissolved in H_2O (50 mL) and subsequently lyophilized. Product was obtained as a white substance (621 mg; 61%; 1 step, based on paraformaldehyde).

NMR (D_2O): ^{1}**H** δ 1.39 (CH_2—C*H*$_2$—CH_2, m, 1H); 1.50 (CH_2—C*H*$_2$—CH_2, m, 3H); 1.57–1.77 (CH_2—C*H*$_2$—CH_2, C*H*$_2$—CH—P, P—C*H*—P, m, 7H); 2.12 (C*H*$_2$—COOH, t, 2H, $^3J_{HH}$ = 7 Hz); 2.51–2.79 (*cycle*, N—C*H*$_2$—P, m, 18H); 7.05 (P*H*, d, $^1J_{HP}$ = 525 Hz); ^{13}**C**{^{1}H} δ 23.8 (*C*H$_2$—CH_2—CH—P, t, $^3J_{CP}$ = 3 Hz); 25.6 (CH_2—*C*H$_2$—CH_2, s); 26.9 (CH_2—*C*H$_2$—CH_2, s); 27.2 (CH_2—*C*H$_2$—CH_2, s); 30.8 (*C*H$_2$—CH—P, dd, $^2J_{CP}$ = 8 Hz, $^2J_{CP}$ = 4 Hz); 38.3 (*C*H$_2$—CO, s); 45.0 (P—*C*H—P, dd, $^1J_{CP}$ = 79 Hz, $^1J_{CP}$ = 73 Hz); 45.8 (*cycle*, s); 46.1 (*cycle*, s); 46.4 (*cycle*, s); 46.7 (*cycle*, s); 47.3 (*cycle*, s);

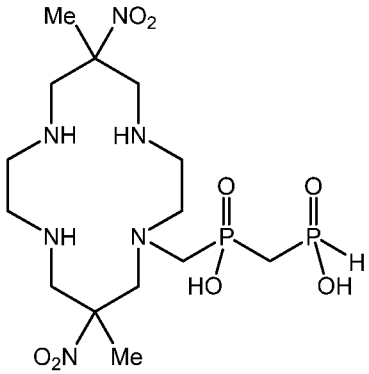
48.2 (*cycle*, s); 53.3 (N—*C*H$_2$—P, d, $^1J_{CP}$ = 103 Hz); 54.1 (*cycle*, d, $^3J_{CP}$ = 7 Hz); 54,7 (*cycle*, d, $^3J_{CP}$ = 6 Hz); 184.6 (*C*O, s); **^{31}P** δ 25.7 (*P*H, dm, 1P, $^1J_{HP}$ = 525 Hz); 36.3 (*P*—CH$_2$—N, m, 1P).

MS: (−) 454.7 [M−H$^+$]$^-$. (+) 457.0 [M+H$^+$]$^+$.

TLC (SiO$_2$, *i*PrOH–conc. NH$_4$OH–H$_2$O 7:1:1): R_f = 0.5.

EA (C$_{14}$H$_{32}$N$_4$O$_5$P$_2$·AcOH, M_R = 516.5): C 44.2 (44.1); H 8.2 (8.5); N 10.9 (10.7).

Example 21: *Synthesis of compound* ***16***



To a glass flask (25 ml), 6,13-dimethyl-6,13-dinitro-1,4,8,11-tetraazacyklotetradecane (411 mg; 885 mmol; 4.7 equiv.) was added. Methylene-bis(phosphinic acid) (61.3 mg; 426 µmol; 2.3 equiv.) and paraformaldehyde (5.6 mg; 187 µmol; 1.0 equiv.) and aqueous HCl (6 M; 10 mL) were subsequently added and the resulting mixture was stirred at 60 °C for two days. The mixture was then evaporated to dryness and several times co-evaporated with H$_2$O. The crude product was purified by ion exchange chromatography (DOWEX 50; 200 mL; H$^+$-form; H$_2$O → 10% aqueous pyridine). Pyridine fraction with product was evaporated to dryness and several times co-evaporated with H$_2$O. The residue was further dried on vaccuum pump and in vaccum dessicator over P$_2$O$_5$. Product was obtained as a yellowish substance (92.2 mg; 82%; 1 step, based on methylene-bis(phosphinic acid)).

NMR (D$_2$O): **^{1}H** δ 1.65 (C*H*$_3$, s, 3H); 1.74 (C*H*$_3$, s, 3H); 2.12 (P—C*H*$_2$—P, dd, 2H, $^2J_{HP}$ = 18 Hz, $^2J_{HP}$ = 16 Hz); 2.69–2.94 (*cycle*, N—C*H*$_2$—P m, 8H); 3.03–3.41 (*cycle*, m, 10H); 7.14 (P*H*, d, 1H, $^1J_{HP}$ = 530 Hz); **^{13}C**{^{1}H} δ 24.2 (*C*H$_3$, s); 25.2 (*C*H$_3$, s); 35.5 (P—*C*H$_2$—P, dd, $^1J_{CP}$ = 79 Hz, $^1J_{CP}$ = 76 Hz); 48.2 (*cycle*, s); 48.8 (*cycle*, s); 49.2 (*cycle*, s); 50.1 (*cycle*, s); 52.3 (*cycle*, s); 52.4 (*cycle*, s); 55.2 (*cycle*, s); 57.6 (N—*C*H$_2$—P, d, $^1J_{CP}$ = 104 Hz); 58.2 (*cycle*, d, $^3J_{CP}$ = 10 Hz); 89.9 (*C*—NO$_2$, s); 91.8

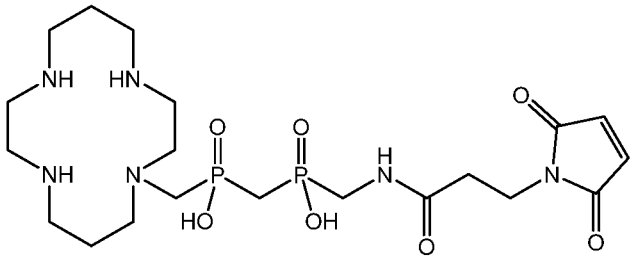
(*C*—NO_2, s); **^{31}P** δ 16.2 (*P*H, dt, 1P, $^1J_{PH}$ = 530 Hz, $^2J_{PH}$ = 18 Hz); 36.9 (N—CH_2—*P*, m, 1P).

MS: (−) 473.3 $[M-H^+]^-$. (+) 475.1 $[M+H^+]^+$; 513.4 $[M+K^+]^+$.

TLC (SiO_2, EtOH–konc. NH_4OH 1:1): R_f = 0.8.

EA ($C_{14}H_{32}N_6O_8P_2 \cdot 3HCl \cdot H_2O$, M_R = 601.8): C 27.9 (27.7); H 6.2 (6.5); N 14.0 (14.3).

Example 22: *Synthesis of conjugate* ***17***



In a glass vial (4 ml), **13**·1.5H_2O (14.1 mg; 34.2 μmol; 1.0 equiv.) and *N*-hydroxysuccinimide ester of 3-(maleimido)propanoic acid (10.0 mg; 37.6 μmol; 1.1 equiv.) were dissolved in aqueous buffer H_3PO_4–NaOH (1.0 M pH = 8.1; 1.00 mL; 1.0 mmol; 29 equiv.). The resulting mixture was stirred at room temperature overnight. The crude product was purified by preparative HPLC (C8; H_2O—MeCN). Fraction with product was lyophilized. Product was obtained as a white substance (13.4 mg; 45%; 1 step, based on **13**·1.5H_2O).

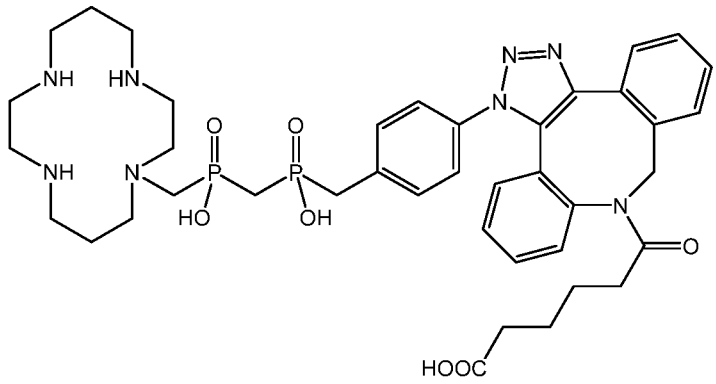
NMR (D_2O): **^{1}H** δ 1.99 (CH_2—CH_2—CH_2, p, 2H, $^3J_{HH}$ = 7 Hz); 2.12 (CH_2—CH_2—CH_2, m, 2H); 2.18 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 16 Hz); 2.48–3.11 (CH_2—CO, N—CH_2—P, *cycle*, m, 20H); 4.21 (CH_2—N—CO, t, $^3J_{HH}$ = 9 Hz); 6.82 (C*H*, s, 2H); **^{13}C**{^{1}H} δ 22.1 (CH_2—*C*H_2—CH_2, s); 23.4 (CH_2—*C*H_2—CH_2, s); 29.8 (*C*H_2—CO, s); 34.1 (P—*C*H_2—P, t, $^1J_{CP}$ = 79 Hz); 43.1 (*C*H_2—N—CO, s); 41.9 (*cycle*, s); 43.6 (*cycle*, s); 43.9 (*cycle*, s); 44.3 (*cycle*, s); 46.8 (*cycle*, s); 47.2 (*cycle*, s); 53.4 (P—*C*H_2—N, d, $^1J_{CP}$ = 96 Hz); 53.6 (*cycle*, s); 55.1 (*cycle*, s); 55.2 (P—*C*H_2—N, d, $^1J_{CP}$ = 108 Hz); 133.7 (*C*H, s); 169.8 (*C*O—N—*C*O, s); 174.5 (CH_2—*C*O—N, d, $^3J_{CP}$ = 5 Hz). **^{31}P**{^{1}H} δ 32.8 (*P*—CH_2—N, d, 1P, $^2J_{PP}$ = 11 Hz); 35.2 (*P*—CH_2—N, d, 1P, $^2J_{PP}$ = 11 Hz).

MS: (−) 535.0 $[M-H^+]^-$. (+) 537.1 $[M+H^+]^+$; 559.1 $[M+Na^+]^+$; 575.1 $[M+K^+]^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 2:1): R_f = 0.5.

EA ($C_{20}H_{38}N_6O_7P_2 \cdot TFA \cdot 2H_2O$, M_R = 869.3): C 30.4 (30.7); H 5.0 (4.7); N 9.7 (9.5).

Example 23: *Synthesis of conjugate* ***18***

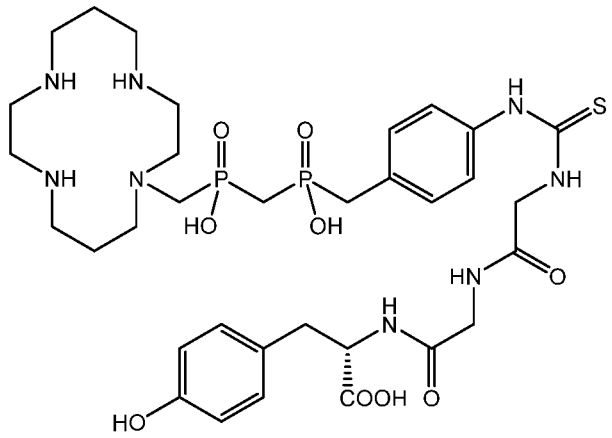


To a glass vial (4 mL), solution of **11**·0.5TFA·1.5H_2O (20.4 mM in D_2O; 420 µL; 8.57 µmol; 1.0 equiv.) was pipetted and, then, freshly prepared solution of 6-dibenzocyclooctynamidehexanoic acid (3.0 mg; 9.0 µmol; 1.1 equiv.) in a mixture of dry DMSO–dry MeCN (1:1; 500 µL) was added. The resulting mixture was stirred at room temperature for 2 hours. The crude product was purified by preparative HPLC (C8; H_2O––MeCN). Fractions with product were lyophilized. Product as two regioisomers was obtained as a white substance (2 × ~3 mg).

NMR (D_2O): **^{1}H** δ 1.18 (C*H*$_2$, m, 2H); 1.32 (C*H*$_2$, m, 2H); 2.04 (*cycle*, p, $^3J_{HH}$ = 6 Hz); 2.15 (*cycle*, P—C*H*$_2$—P, C*H*$_2$, m, 6H); 2.36 (C*H*$_2$, m, 1H); 2.56 (C*H*$_2$, m, 1H); 2.67–3.63 (*cycle*, N—C*H*$_2$—P, P—C*H*$_2$—C, m, 20H); 5.07 (C*H*$_2$—N—CO, d, 1H, $^2J_{HH}$ = 18 Hz); 5.67 (C*H*$_2$—N—CO, d, 1H, $^2J_{HH}$ = 18 Hz); 6.89 (C*H*, d, 1H, $^3J_{HH}$ = 8 Hz); 7.21 (C*H*, t, 1H, $^3J_{HH}$ = 8 Hz); 7.29 (C*H*, d, 1H, $^3J_{HH}$ = 8 Hz); 7.39 (C*H*, m, 1H); 7.42 (C*H*, m, 1H); 7.45 (C*H*—C—CH$_2$—P, d, 2H, $^3J_{HH}$ = 8 Hz); 7.50 (C*H*—C—N$_3$, C*H*, m, 3H); 7.55 (C*H*, m, 2H); **^{13}C**{^{1}H} δ 23.0 (*cycle*, s); 23.3 (*cycle*, s); 24.3 (*C*H$_2$, s); 24.6 (*C*H$_2$, s); 32.4 (P—*C*H$_2$—P, t, $^1J_{CP}$ = 80 Hz); 33.3 (*C*H$_2$, s); 34.1 (*C*H$_2$, s); 40.2 (P—*C*H$_2$—P, d, $^1J_{CP}$ = 89 Hz); 42.9 (*cycle*, s); 44.2 (*cycle*, s); 44.9 (*cycle*, s); 45.4 (*cycle*, s); 46.0 (*cycle*, s); 46.4 (*cycle*, s); 53.6 (N—*C*H$_2$—P, d, $^1J_{CP}$ = 106 Hz); 55.0 (*cycle*, s); 55.9 (*cycle*, d, $^3J_{CP}$ = 11 Hz); 55.9 (C*H*$_2$—N—CO, s); 116.1–145.2 (4 × *arom.*, 14 × *arom.*); 177.1 (*C*O—N, s); 178.9 (*C*O—O, s); **^{31}P**{^{1}H} δ 30.9 (CH$_2$—*P*—CH$_2$, m, 1P); 34.5 (CH$_2$—*P*—CH$_2$, d, 1P, $^2J_{PP}$ = 10 Hz).

MS: (–) 818.8 [M–H$^+$]$^-$. (+) 821.1 [M+H$^+$]$^+$; 843.0 [M+Na$^+$]$^+$; 859.0 [M+K$^+$]$^+$.

Example 24: *Synthesis of targeting conjugate* ***19***

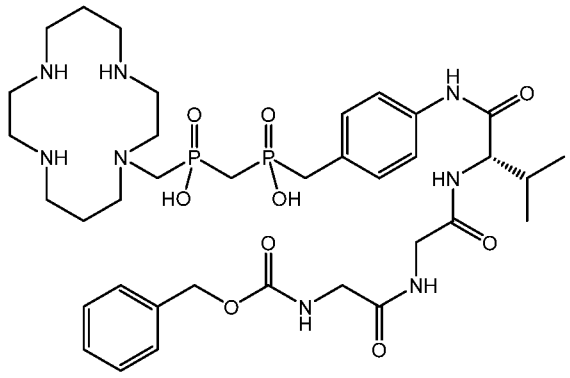


In an NMR tube, **10**·TFA·3.5H_2O (3.4 mg; 3.9 μmol; 1.0 equiv.) was dissolved in D_2O (500 μL). The HGlyGlyTyrOH (1.9 mg; 6.2 μmol; 1.6 equiv.) and aqueous buffer H_3BO_3–LiOH (750 mM in D_2O; pD = 9.3; 413 μL; 310 μmol; 80 equiv.) were then added and the mixture was stirred at room temperature overnight. The crude product was purified by preparative HPLC (C8; H_2O—MeCN). Fraction with product was lyophilized. Product was obtained as a white substance (~1 mg).

NMR (D_2O): **^{1}H** δ 2.01 (CH_2—CH_2—CH_2, m, 2H); 2.06 (CH_2—CH_2—CH_2, m, 2H); 2.12 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 15 Hz); 2.58–3.56 (*cycle*, N—CH_2—P, P—CH_2—C, CH_2, m, 22H); 3.90 (CH_2, m, 2H); 4.21 (CH_2, m, 2H); 4.64 (C*H*—N, dd, 1H, $^3J_{HH}$ = 9 Hz, $^3J_{HH}$ = 5 Hz); 6.85 (C*H*—C—OH, d, 2H, $^3J_{HH}$ = 8 Hz); 7.16 (CH—C*H*—CH_2, d, 2H, $^3J_{HH}$ = 8 Hz); 7.32 (C*H*—C—NH, d, 2H, $^3J_{HH}$ = 8 Hz); 7.38 (C*H*—C—CH_2, d, 2H, $^3J_{HH}$ = 8 Hz); **^{13}C**{^{1}H} δ 23.0 (CH_2—*C*H_2—CH_2, s); 23.8 (CH_2—*C*H_2—CH_2, s); 32.4 (P—*C*H_2—P, t, $^1J_{CP}$ = 80 Hz); 36.5 (*C*H_2, s); 40.1 (P—*C*H_2—C, d, $^1J_{CP}$ = 89 Hz); 42.9 (*C*H_2, s); 43.3 (*cycle*, s); 44.8 (*cycle*, s); 45.6 (*cycle*, s); 46.0 (*cycle*, s); 46.4 (*cycle*, s); 47.0 (*cycle*, s); 48.2 (*C*H_2, s); 53.5 (P—*C*H_2—N, d, $^1J_{CP}$ = 107 Hz); 54.9 (*cycle*, s); 55.1 (*C*H—N, s); 55.8 (*cycle*, d, $^3J_{CP}$ = 11 Hz); 116.1 (*C*H—C—OH, s); 126.8 (*C*H—C—NH, s); 129.2 (*C*—CH_2, s); 131.3 (*C*H—C—CH_2, s); 131.5 (*C*H—C—CH_2, s); 134.3 (*C*—CH_2—P, d, $^2J_{CP}$ = 6 Hz); 135.8 (C—NH, s); 155.1 (*C*—OH, s); 171.9 (*C*O, s); 173.1 (*C*O, s); 175.7 (*C*O, s); 182.3 (*C*S, s); **^{31}P**{^{1}H} δ 31.2 (N—CH_2—*P*, m, 1P); 34.2 (*P*—CH_2—C, d, 1P, $^2J_{PP}$ = 8 Hz).

MS: (−) 796.8 $[M-H^+]^-$. (+) 799.0 $[M+H^+]^+$.

Example 25: *Synthesis of targeting conjugate* ***20***

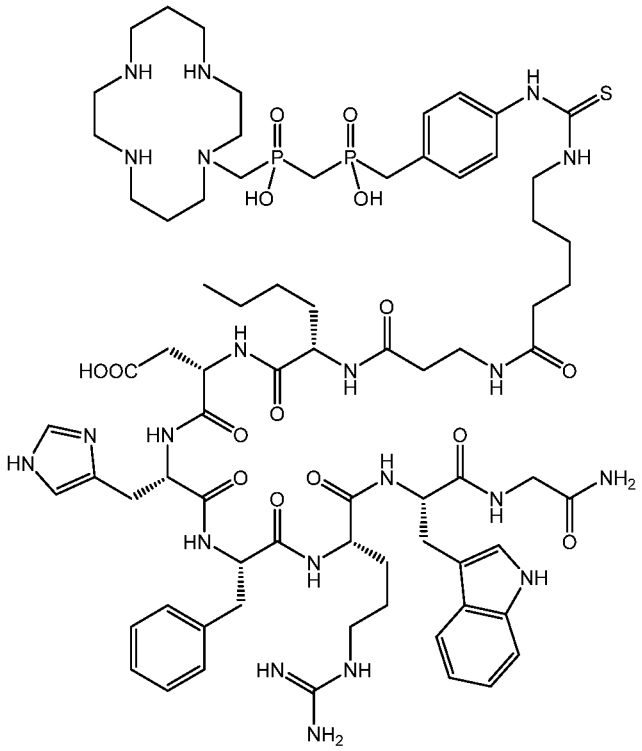


In a glass vial (4 mL), HOValGlyGlyCbz (9.6 mg; 26 μmol; 3.0 equiv.) was dissolved in H_2O–MeCN (2:3; 1.0 mL). Trichlortriazine (1.6 mg; 8.7 μmol; 1.0 equiv.) and pyridine (21.2 μL; 0.26 mmol; 30 equiv.) were subsequently added and the resulting mixture was stirred at room temperature for one hour. Solution of **9**·3H_2O (17.4 mg; 33.8 μmol; 3.9 equiv.) in a mixture of H_2O–MeCN (2:3; 1.0 mL) was then added and the resulting mixture was further stirred at room temperature overnight. The crude product was purified by preparative HPLC (C8; H_2O—MeCN). Fraction with product was lyophilized. Product was obtained as a white substance (~1 mg).

NMR (D_2O): **^{1}H** δ 1.02 (CH_3, m, 6H); 2.02 (CH_2—CH_2—CH_2, p, 2H, $^3J_{HH}$ = 6 Hz); 2.07 (CH_2—CH_2—CH_2, p, 2H, $^3J_{HH}$ = 6 Hz); 2.16 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 16 Hz); 2.20 (CH_3—C*H*—CH_3, m, 1H); 2.34–3.52 (*cycle*, N—CH_2—P, P—CH_2—C, bm, 20H); 3.91 (CH_2, s, 2H); 4.02 (CH_2, s, 2H); 4.23 (C*H*—CO, d, 1H, $^3J_{HH}$ = 8 Hz); 5.15 (Ph—CH_2—O, s, 2H); 7.29–7.51 (C*H*—C—N, C*H*—C—CH_2, *Ph*, bm, 9H); **^{13}C**{^{1}H} δ 18.5 (*C*H_3, s); 19.1 (*C*H_3, s); 23.0 (CH_2—*C*H_2—CH_2, s); 23.6 (CH_2—*C*H_2—CH_2, s); 31.0 (CH_3—*C*H—CH_3, s); 32.5 (P—*C*H_2—P, t, $^1J_{CP}$ = 80 Hz); 40.0 (P—*C*H_2—C, d, $^1J_{CP}$ = 90 Hz); 43.1 (*C*H_2, s); 43.2 (*cycle*, s); 44.5 (*C*H_2, s); 44.6 (*cycle*, s); 45.4 (*cycle*, s); 45.6 (*cycle*, s); 46.3 (*cycle*, s); 46.6 (*cycle*, s); 53.5 (P—*C*H_2—N, d, $^1J_{CP}$ = 107 Hz); 54.8 (*cycle*, s); 55.8 (*cycle*, d, $^3J_{CP}$ = 10 Hz); 61.1 (*C*H—CO, s); 68.1 (Ph—*C*H_2—O, s); 123.3 (*Ph*, s); 128.5 (*C*H—C—NH, s); 129.2 (*Ph*, s); 129.6 (*Ph*, s); 131.2 (*C*H—C—CH_2, d, $^3J_{CP}$ = 6 Hz); 132.5 (*C*—CH_2—P, d, $^2J_{CP}$ = 8 Hz); 135.4 (C—NH, s); 137.0 (*Ph*, s); 159.4 (*C*O—O, s); 172.3 (*C*O, s); 173.0 (*C*O, s); 173.9 (*C*O, s); **^{31}P**{^{1}H} δ 30.1 (N—CH_2—*P*, m, 1P); 34.4 (*P*—CH_2—C, d, 1P, $^2J_{PP}$ = 9 Hz).

MS: (−) 806.9 $[M-H^+]^-$. (+) 809.1 $[M+H^+]^+$; 831.0 $[M+Na^+]^+$.

Example 26: *Synthesis of targeting conjugate* ***21***

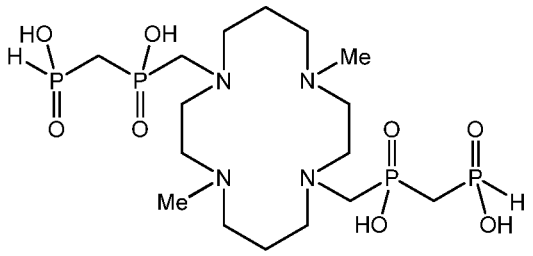


To a glass vial (4 mL), **10**·TFA·3.5H_2O (13.2 mg; 18.5 μmol; 1.7 equiv.) was added. Peptide $NH_2(CH_2)_5CONH(CH_2)_2CONleAspHis^D$-PheArgTrpGly$NH_2$ (12.0 mg; 10.8 μmol; 1.0 equiv.) and aqueous buffer H_3BO_3–LiOH (750 mM in D_2O; pD = 9.3; 3.5 mL; 2.63 mmol; 240 equiv.) were subsequently added and the resulting mixture was stirred at room temperature overnight. The crude product was purified by preparative HPLC (C8; H_2O—MeCN). Fraction with product was lyophilized. Product was obtained as a white substance (~2 mg).

NMR (D_2O): **^{1}H** δ 0.83 (C*H*$_3$, t, 3H, $^3J_{HH}$ = 7 Hz); 1.04 (CH_2, bm, 2H); 1.21–1.72 (CH_2, bm, 10H); 1.82–2.23 (P—C*H*$_2$—P, C*H*$_2$, *cycle*, bm, 8H); 2.35–3.54 (*cycle*, C*H*$_2$, P—C*H*$_2$—N, P—C*H*$_2$—C, bm, 38H); 3.80 (C*H*$_2$, m, 2H); 4.12 (C*H*, m, 1H); 4.16 (C*H*, m, 1H); 4.51 (C*H*, m, 1H); 4.55 (C*H*, m, 1H); 4.59 (C*H*, m, 1H); 4.69 (C*H*, m, 1H); 7.06 (CH_2—C—C*H*—N, s, 1H); 7.10–7.27 (*arom.*, m, 7H); 7.28–7.39 (*arom.*, m, 5H); 7.46 (C*H*, d, 1H, $^3J_{HH}$ = 7 Hz); 7.63 (C*H*, d, 1H, $^3J_{HH}$ = 8 Hz); 8.53 (N—C*H*—N, s, 1H); **^{31}P**{^{1}H} δ 32.5 (CH_2—*P*—CH_2, m, 1P); 35.4 (CH_2—*P*—CH_2, m, 1P).

MS: (–) 1614.5 $[M-H^+]^-$. (+) 1616.4 $[M+H^+]^+$.

Example 27: *Synthesis of compound* ***22***



To a glass vial (4 mL), **3**·3.5H_2O (35.6 mg; 79.6 μmol; 1.0 equiv.) was added. Methylene-bis(phosphinic acid) (27.6 mg; 192 μmol; 2.4 equiv.), paraformaldehyde (5.8 mg; 193 μmol; 2.4 equiv.) and aqueous HCl (6 M; 1 mL) were subsequently added and the resulting suspension was stirred overnight at 80 °C. The mixture was evaporated to dryness and the residue was several times co-evaporated with H_2O. The crude product was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O). Fractions with product were combined, evaporated to dryness and further co-evaporated with H_2O. Residue was re-dissolved in H_2O (50 mL) and subsequently lyophilized. Product was obtained as a white substance (21.2 mg; 47%; 1 step, based on **3**·3.5H_2O).

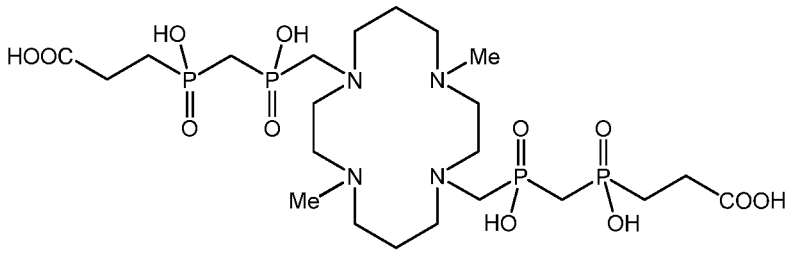
NMR (D_2O): **^{1}H** δ 1.71 (CH_2—CH_2—CH_2, p, 4H, $^3J_{HH}$ = 7 Hz); 2.04 (P—CH_2—P, dd, 2H, $^2J_{HP}$ = 18 Hz, $^2J_{HP}$ = 16 Hz); 2.23 (CH_3, s, 6H); 2.51 (*cycle*, t, 4H, $^3J_{HH}$ = 7 Hz); 2.57 (*cycle*, m, 4H); 2.75 (*cycle*, m, 4H); 2.81 (N—CH_2—P, d, 2H, $^2J_{HP}$ = 9 Hz); 2.86 (*cycle*, m, 4H); 7.13 (P*H*, d, $^1J_{HP}$ = 531 Hz); **^{13}C**{^{1}H} δ 20.2 (CH_2—*C*H_2—CH_2, s); 35.7 (P—*C*H_2—P, t, $^1J_{CP}$ = 77 Hz); 44.0 (*C*H_3, s); 48.7 (*cycle*, s); 49.9 (*cycle*, d, $^3J_{CP}$ = 7 Hz); 51.9 (*cycle*, d, $^3J_{CP}$ = 7 Hz); 53.8 (*cycle*, s); 57.0 (N—*C*H_2—P, d, $^1J_{CP}$ = 110 Hz); **^{31}P** δ 19.8 (*P*H, dtd, 2P, $^1J_{PH}$ = 531 Hz, $^2J_{PH}$ = 18 Hz, $^2J_{PP}$ = 3 Hz); 32.0 (N—CH—*P*, m, 2P).

MS: (−) 539.3 [M−H^+]$^-$. (+) 541.4 [M+H^+]$^+$; 563.4 [M+Na^+]$^+$; 585.4 [M−H^++2Na^+]$^+$; 607.4 [M−2H^++3Na^+]$^+$.

TLC (SiO_2, *i*-PrOH–conc. NH_4OH–H_2O 7:3:3): R_f = 0.7.

EA ($C_{16}H_{40}N_4O_8P_4$·1.5H_2O, M_R = 567.4): C 33.9 (33.8); H 7.6 (7.2); N 9.9 (9.6).

Example 28: *Synthesis of compound* ***23***



To a glass vial (20 ml), 1,8-dimethyl-1,4,8,11-tetraazacyclotetradecane tetrahydrochloride (295 mg; 788 μmol; 1.0 equiv.) was added. Intermediate **D** (792 mg; 3,66 mmol; 4,6 equiv.), paraformaldehyde (49.7 mg; 1.66 mmol; 2.1 equiv.) and aqueous HCl (6 M; 15 mL) were subsequently added and the resulting suspension was stirred at 80 °C for three days. Mixture was then evaporated to dryness and several times co-evaporated with H_2O. The crude product was purified by column chromatography (SiO_2; EtOH–conc. aq. NH_4OH 1:1; $R_f = 0.5$). Fractions with product were joined and evaporated to dryness. Residue was re-dissolved in H_2O (25 mL), treated with charcoal and resulting suspension was filtered through syringe microfilter (Millipore; 0.22 μm). Filtrate was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O). Fractions with product were combined and evaporated to dryness. The residue was re-dissolved in H_2O (500 mL) and subsequently lyophilized. Product was obtained as a white substance (392 mg; 62 %; 1 step, based on 1,8-dimethyl-1,4,8,11-tetraazacyclotetradecane tetrahydrochloride).

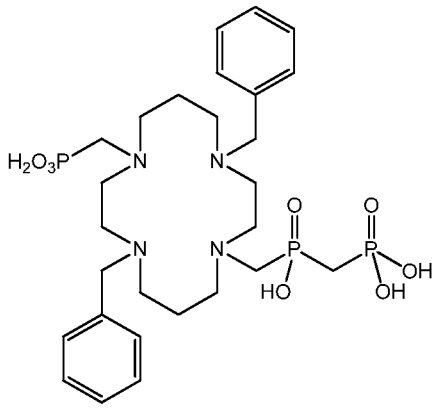
NMR (D_2O): **^{1}H** δ 1.80 (CH_2—C*H*$_2$—CH_2, p, 4H, $^3J_{HH}$ = 6 Hz); 1.95 (P—C*H*$_2$—C, m, 4H); 2.10 (P—C*H*$_2$—P, dd, 4H, $^2J_{HP}$ = 17 Hz, $^2J_{HP}$ = 15 Hz); 2.25 (C*H*$_3$, s, 6H); 2.35 (C*H*$_2$—CO, tm, 4H, $^3J_{HH}$ = 8 Hz); 2.49 (*cycle*, t, 4H, $^3J_{HH}$ = 7 Hz); 2.51 (*cycle*, m, 2H); 2.58 (*cycle*, m, 4H); 2.63–2.79 (*cycle*, N—C*H*$_2$—P, m, 10H); **^{13}C**{^{1}H} δ 23.2 (CH_2—*C*H$_2$—CH_2, s); 29.2 (P—*C*H$_2$—C, d, $^1J_{CP}$ = 97 Hz); 30.8 (*C*H$_2$—CO, s); 31.0 (P—*C*H$_2$—P, dd, $^1J_{CP}$ = 79; $^1J_{CP}$ = 76 Hz); 43.8 (*C*H$_3$, s); 50.2 (*cycle*, d, $^3J_{CP}$ = 6 Hz); 50.6 (*cycle*, s); 52.6 (*cycle*, s); 54.2 (*cycle*, s); 55.5 (N—*C*H$_2$—P, d, $^1J_{CP}$ = 110 Hz); 184.1 (*C*O, d, $^3J_{CP}$ = 17 Hz); **^{31}P**{^{1}H} δ 33.8 (CH_2—*P*—CH_2, d, 1P, $^2J_{PP}$ = 9 Hz); 34.8 (CH_2—*P*—CH_2, d, 1P, $^2J_{PP}$ = 9 Hz).

MS: (−) 665.2 [M−H_3O^+]$^-$; 683.3 [M−H^+]$^-$. (+) 685.2 [M+H^+]$^+$; 707.2 [M+Na^+]$^+$; 729.2 [M−H^++2Na^+]$^+$; 751.1 [M−2H^++3Na^+]$^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 1:1): $R_f = 0.5$.

EA ($C_{22}H_{48}N_4O_{12}P_4 \cdot 3H_2O$, M_R = 738.6): C 35.8 (35.5); H 7.6 (8.0); N 7.6 (7.7).

Example 29: *Synthesis of compound* ***24***



To a glass vial (4 ml), **6**·3.5HCl·H_2O (81.3 mg; 116 μmol; 1.0 equiv.) was added. Phosphorous acid (90.2 mg; 1.10 mmol; 9.5 equiv.), paraformaldehyde (8.2 mg; 273 μmol; 2.4 equiv.) and aqueous HCl (12 M; 1 mL) were subsequently added and the resulting suspension was stirred at 40 °C for five days. The mixture was then evaporated to dryness and several times co-evaporated with H_2O. The residue was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O). Fractions with product were combined and evaporated to dryness. The residue was several times co-evaporated with H_2O and re-dissolved in H_2O (50 mL). The resulting solution was subsequently lyophilized. Product was obtained as a white substance (40.4 mg; 51 %; 1 step, based on **6**·3.5HCl·H_2O).

NMR (D_2O): **^{1}H** δ 1.78–1.94 (CH_2—CH_2—CH_2, bm, 4H); 2.12 (P—CH_2—P, dd, 2H, $^2J_{HP}$ = 19 Hz, $^2J_{HP}$ = 17 Hz); 2.51–2.60 (*cycle*, m, 2H); 2.63–2.81 (*cycle*, bm, 4H); 2.88–2.98 (*cycle*, N—CH_2—P, m, 4H); 3.03–3.44 (*cycle*, N—CH_2—P, m, 10H); 3.94 (CH_2—Ph, bm, 2H); 4.02 (CH_2—Ph, bm, 2H); 6.99–7.30 (*Ph*, m, 8H); **^{13}C**{^{1}H} δ 22.6 (CH_2—*C*H_2—CH_2, s); 27.6 (CH_2—*C*H_2—CH_2, s); 34.8 (P—*C*H_2—P, dd, $^1J_{CP}$ = 117 Hz, $^1J_{CP}$ = 75 Hz); 41.5 (*cycle*, s); 42.4 (*cycle*, s); 50.4 (*cycle*, s); 51.3 (*cycle*, s); 52.3 (*cycle*, s); 52.9 (N—*C*H_2—P, d, $^1J_{CP}$ = 104 Hz); 53.3 (*cycle*, s); 54.8 (*cycle*, s); 56.2 (*C*H_2—Ph, s); 56.9 (*cycle*, d, $^3J_{CP}$ = 8 Hz); 58.9 (*C*H_2—Ph, s); 59.0 (N—*C*H_2—P, d, $^1J_{CP}$ = 110 Hz); 123.3 (*Ph*, s); 124.5 (*Ph*, s); 129.0 (*Ph*, s); 129.2 (*Ph*, s); 130.3 (*Ph*, s); 131.4 (*Ph*, s); 137.2 (*Ph*, s); 142.8 (*Ph*, s);

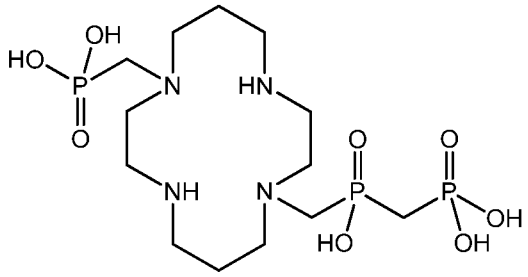
^{31}P{^{1}H} 19.2 (HO—*P*—OH, m, 1P); 26.9 (HO—*P*—OH, d, 1P, $^2J_{PP}$ = 9 Hz); 34.5 (N—CH—*P*, bm, 1P).

MS: (−) 645.0 $[M-H^+]^-$. (+) 647.1 $[M+H^+]^+$; 669.2 $[M+Na^+]^+$; 685.2 $[M+K^+]^+$.

TLC (SiO_2, *i*PrOH–conc. NH_4OH–H_2O 7:3:3): R_f = 0.8.

EA ($C_{27}H_{45}N_4O_8P_3 \cdot 2H_2O$, M_R = 682.6): C 47.5 (47.6); H 7.2 (7.2); N 8.2 (8.2).

Example 30: *Synthesis of compound* ***25***



In a glass flask (50 ml), **24**·$2H_2O$ (26.3 mg; 38.5 μmol; 1.0 equiv.) was dissolved in H_2O (25 mL) and the resulting mixture was briefly washed with gaseous argon. Ammonium formate (98.2 mg; 1.56 mmol; 41 equiv.) and Pd@C catalyst (10 %; 9.1 mg) were subsequently added. Resulting suspension was stirred at 60 °C overnight. The mixture was then evaporated to dryness and several times co-evaporated with H_2O. The residue was dissolved in H_2O, the catalyst was filtered off and the filtrate was evaporated to dryness. The residue was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O). Aqueous fraction with product was evaporated to dryness and several times co-evaporated with H_2O. The residue was re-dissolved in H_2O (50 mL) and lyophilized. Product was obtained as a white substance (15.4 mg; 76%; 1 step, based on **24**·$2H_2O$).

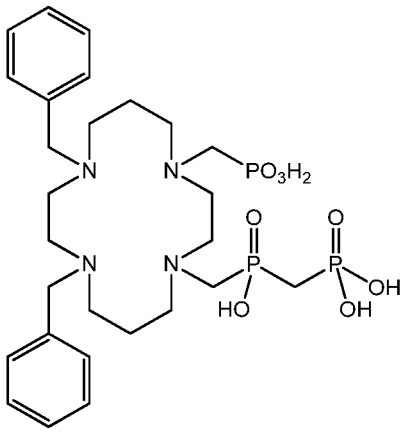
NMR (D_2O): ^{1}**H** δ 1.85–1.98 (CH_2—CH_2—CH_2, bm, 4H); 2.11 (P—CH_2—P, dd, 2H, $^2J_{HP}$ = 18 Hz, $^2J_{HP}$ = 15 Hz); 2.48–2.84 (*cycle*, bm, 6H); 2.88 (*cycle*, m, 2H); 3.01 (N—CH_2—P, d, 2H, $^2J_{HP}$ = 12 Hz); 3.08–3.38 (*cycle*, N—CH_2—P, m, 10H); ^{13}**C**{^{1}H} δ 23.1 (CH_2—CH_2—CH_2, s); 27.4 (CH_2—CH_2—CH_2, s); 34.2 (P—CH_2—P, dd, $^1J_{CP}$ = 117 Hz, $^1J_{CP}$ = 76 Hz); 43.8 (*cycle*, s); 42.4 (*cycle*, s); 50.4 (*cycle*, s); 51.3 (*cycle*, s); 52.6 (*cycle*, s); 52.8 (N—CH_2—P, d, $^1J_{CP}$ = 107 Hz); 54.1 (*cycle*, s); 55.2 (*cycle*, s); 57.6 (N—CH_2—P, d, $^1J_{CP}$ = 111 Hz); 58.2 (*cycle*, d, $^3J_{CP}$ = 8 Hz); ^{31}**P**{^{1}H} 28.3 (HO—*P*—OH, d, 1P, $^2J_{PP}$ = 10 Hz); 32.6 (N—CH—*P*, d, 1P, $^2J_{PP}$ = 10 Hz).

MS: (−) 465.2 $[M-H^+]^-$. (+) 467.3 $[M+H^+]^+$; 489.2 $[M+Na^+]^+$; 505.2 $[M+K^+]^+$; 511.2 $[M-H^+ +2Na^+]^+$.

TLC (SiO_2, *i*PrOH–conc. aq. NH_4OH–H_2O 7:3:3): R_f = 0.4.

EA ($C_{13}H_{33}N_4O_8P_3 \cdot 3.5H_2O$, M_R = 529.4): C 29.5 (29.3); H 7.6 (7.9); N 10.6 (10.7).

Example 31: *Synthesis of compound* ***26***



To a glass vial (4 ml), **7**·4H_2O (91.3 mg; 150 μmol; 1.0 equiv.) was added. Phosphorous acid (123 mg; 1.5 mmol; 10 equiv.), paraformaldehyde (10.8 mg; 360 μmol; 2.4 equiv.) and aqueous HCl (12 M; 1 mL) were subsequently added and the resulting suspension was stirred at 40 °C for five days. The mixture was then evaporated to dryness and several times co-evaporated with H_2O. The residue was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O). Fractions with product were joined and evaporated to dryness. The residue was several times co-evaporated with H_2O and re-dissolved in H_2O (50 mL). Resulting solution was subsequently lyophilized. Product was obtained as a white substance (59.4 mg; 58 %; 1 step, based on **7**·4H_2O).

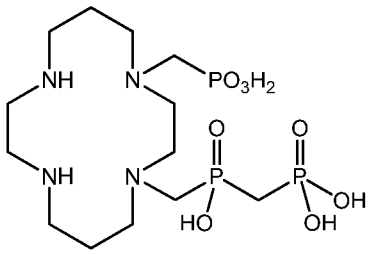
NMR (D_2O): 1.72–1.84 (CH_2—C*H*$_2$—CH_2, bm, 2H); 1.92 (CH_2—C*H*$_2$—CH_2, m, 1H); 2.05–2.33 (CH_2—C*H*$_2$—CH_2, P—C*H*$_2$—P bm, 3H); 2.49–3.24 (*cycle*, N—C*H*$_2$—P, bm, 20H); 3.82 (C*H*$_2$—Ph, m, 2H); 4.07 (C*H*$_2$—Ph, m, 2H); 6.83–6.92 (*Ph*, bm, 3H); 6.98–7.22 (*Ph*, bm, 8H); ^{31}**P**{^{1}H} 18.3 (HO—*P*—OH, s, 1P); 22.9 (HO—*P*—OH, d, 1P, $^2J_{PP}$ = 9 Hz); 32.4 (N—CH—*P*, bm, 1P).

MS: (−) 645.1 [M−H^+]$^-$. (+) 647.4 [M+H^+]$^+$; 669.5 [M+Na^+]$^+$; 685.4 [M+K^+]$^+$.

TLC (SiO_2, *i*PrOH–conc. NH_4OH–H_2O 7:3:3): R_f = 0.8.

EA ($C_{27}H_{45}N_4O_8P_3$·2H_2O, M_R = 682.6): C 47.2 (47.6); H 7.3 (7.2); N 8.0 (8.2).

Example 32: *Synthesis of compound* ***27***



In a glass flask (50 ml), **26**·2H_2O (28 mg; 41 μmol; 1.0 equiv.) was dissolved in H_2O (25 mL) and the resulting mixture was briefly washed with gaseous argon. Ammonium formate (107.8 mg; 1.71 mmol; 45 equiv.) and Pd@C catalyst (10 %; 9.1 mg) were subsequently added. The resulting suspension was stirred at 60 °C overnight. The mixture was then evaporated to dryness and several times evaporated with H_2O. The residue was dissolved in H_2O, the catalyst was filtered off and the filtrate was evaporated to dryness. The residue was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O). Aqueous fraction with product was evaporated to dryness and several times co-evaporated with H_2O. The residue was re-dissolved in H_2O (50 mL) and lyophilized. Product was obtained as a white substance (15.4 mg; 82%; 1 step, based on **26**·2H_2O).

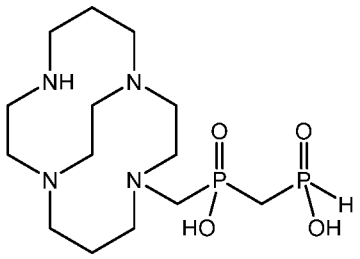
NMR (D_2O): **NMR** (D_2O): **^{1}H** δ 1.88 (CH_2—CH_2—CH_2, m, 1H); 1.97–2.08 (CH_2—CH_2—CH_2, bm, 2H); 2.13–2.35 (P—CH_2—P, CH_2—CH_2—CH_2, bm, 3H); 2.44–3.38 (*cycle*, N—CH_2—P, m, 20H); **^{13}C**{^{1}H} δ 22.8 (CH_2—CH_2—CH_2, s); 25.2 (CH_2—CH_2—CH_2, s); 33.1 (P—CH_2—P, dd, $^1J_{CP}$ = 114 Hz, $^1J_{CP}$ = 80 Hz); 42.1 (*cycle*, s); 45.5 (*cycle*, s); 49.9 (*cycle*, s); 51.1 (*cycle*, s); 51.5 (*cycle*, s); 53.9 (N—CH_2—P, d, $^1J_{CP}$ = 109 Hz); 54.6 (*cycle*, s); 54.8 (*cycle*, s); 57.6 (*cycle*, s); 59.2 (N—CH_2—P, d, $^1J_{CP}$ = 108 Hz); **^{31}P**{^{1}H} 21.3 (HO—*P*—OH, m, 1P); 28.3 (HO—*P*—OH, d, 1P, $^2J_{PP}$ = 10 Hz); 32.2 (N—CH—*P*, d, 1P, $^2J_{PP}$ = 10 Hz).

MS: (−) 465.4 [M−H^+]$^-$. (+) 467.2 [M+H^+]$^+$; 489.5 [M+Na^+]$^+$; 505.5 [M+K^+]$^+$; 511.6 [M−H^++2Na^+]$^+$.

TLC (SiO_2, *i*PrOH–conc. NH_4OH–H_2O 7:3:3): R_f = 0.4.

EA ($C_{13}H_{33}N_4O_8P_3$·5H_2O, M_R = 556.4): C 28.3 (28.1); H 8.6 (8.8); N 9.8 (10.1).

Example 33: *Synthesis of compound* ***28***



To a glass vial (20 ml), 1,4,8,11-tetraazabicyklo[6.6.2]hexadecane (1.17 g; 5.16 mmol; 2.4 equiv.) was added. Methylene-bis(phosphinic acid) (633 mg; 4.40 mmol; 2.0 equiv.), paraformaldehyde (65.3 mg; 2.17 mmol; 1.0 equiv.) and aqueous HCl (5 M; 20 mL) were subsequently added and the resulting suspension was stirred 80 °C overnight. The mixture was then evaporated to dryness and several times co-evaporated with H_2O. The residue was purified by ion exchange chromatography (Amberlite IRA 402; OH^--form; $H_2O \rightarrow$ 10 % aqueous AcOH). Acetate fraction with product was evaporated to dryness and several times co-evaporated with H_2O. The residue was dissolved in aqueous HCl (5 M; 10 mL) and the resulting solution was evaporated to dryness. The residue was further dried on vacuum pump and then in vacuum desiccator over P_2O_5. The final product was obtained as a white substance (668 mg; 63%; 1 step; based on paraformaldehyde).

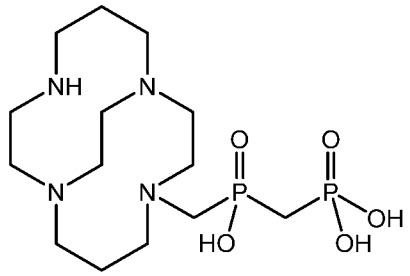
NMR (D_2O): **^{1}H** δ 1.70 (CH_2—C*H*$_2$—CH_2, dm, 1H, $^1J_{HH}$ = 17 Hz); 1.76 (CH_2—C*H*$_2$—CH_2, dm, 1H, $^1J_{HH}$ = 17 Hz); 2.12 (P—C*H*$_2$—P, m, 2H); 2.30 (CH_2—C*H*$_2$—CH_2, m, 1H); 2.30 (CH_2—C*H*$_2$—CH_2, m, 1H); 2.56 (*cycle*, m, 2H); 2.63 (*cycle*, m, 2H); 2.92 (*cycle*, m, 3H); 3.05 (*cycle*, m, 2H); 3.14 (*cycle*, m, 2H); 3.17 (N—C*H*$_2$—P, 1H); 3.22 (*cycle*, m, 1H); 3.30 (*cycle*, m, 3H); 3.44 (*cycle*, m, 2H); 3.62 (*cycle*, m, 1H); 3.73 (N—C*H*$_2$—P, m, 1H); 3.78 (*cycle*, m, 2H); 7.13 (P*H*, d, 1H, $^1J_{HP}$ = 533 Hz); **^{13}C**{^{1}H} δ 18.9 (CH_2—C*H*$_2$—CH_2, s); 20.1 (CH_2—C*H*$_2$—CH_2, s); 36.0 (P—C*H*$_2$—P, dd, $^1J_{CP}$ = 84 Hz; $^1J_{CP}$ = 77 Hz); 42.2 (*cycle*, s); 47.7 (*cycle*, s); 49.5 (*cycle*, s); 49.9 (*cycle*, s); 51.7 (C*H*$_2$—N—CH_2—P, d, $^3J_{CP}$ = 6 Hz); 54.0 (N—C*H*$_2$—P, d, $^1J_{CP}$ = 91 Hz); 54.4 (*cycle*, s); 56.2 (*cycle*, s); 58.2 (*cycle*, s); 58.4 (*cycle*, s); 59.5 (*cycle*, s); **^{31}P** δ 20.6 (*P*H, dtd, 1P, $^1J_{PH}$ = 533 Hz, $^2J_{PH}$ = 17 Hz, $^2J_{PP}$ = 6 Hz); 25.7 (*P*—CH_2—N, m, 1P).

MS: (−) 381.2 [M−H$^+$]$^-$; 402.9 [M−2H$^+$+Na$^+$]$^-$. (+) 383.3 [M+H$^+$]$^+$; 405.3 [M+Na$^+$]$^+$; 421.2 [M+K$^+$]$^+$.

TLC (SiO_2, *i*PrOH–conc. aq. NH_4OH–H_2O 7:3:3): R_f = 0.7.

EA ($C_{14}H_{32}N_4O_4P_2 \cdot 2.5HCl \cdot H_2O$, M_R = 491.5): C 34.2 (34.4); H 7.5 (7.7); N 11.4 (11.0).

Example 34: *Synthesis of compound* ***29***



To a glass vial (50 ml), 1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (954 mg; 4.22 mmol; 2.0 equiv.) was added. Intermediate **A**·0.5H_2O (360 mg; 2.13 mmol; 1.0 equiv.), paraformaldehyde (81.9 mg; 2.73 mmol; 1.3 equiv.) and aqueous HCl (5 M; 20 mL) were subsequently added and the resulting suspension was stirred 80 °C overnight. The mixture was then evaporated to dryness and several times co-evaporated with H_2O. The residue was purified by ion exchange chromatography (Amberlite IRA 402; OH^--form; $H_2O \rightarrow$ 10 % aqueous AcOH). Acetate fraction with product was evaporated to dryness and several times co-evaporated with H_2O. The residue was dissolved in aqueous HCl (6 M; 10 mL) and the resulting solution was evaporated to dryness. The residue was further dried on vacuum pump and in later in vacuum desiccator over P_2O_5. The final product was obtained as a white substance (571 mg; 58%; 1 step; based on **A**·0.5H_2O).

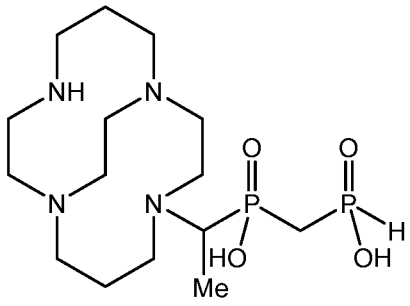
NMR (D_2O): **^{1}H** δ 1.66 (CH_2—CH_2—CH_2, dm, 1H, $^1J_{HH}$ = 17 Hz); 1.75 (CH_2—CH_2—CH_2, dm, 1H, $^1J_{HH}$ = 17 Hz); 1.92 (P—CH_2—P, m, 2H); 2.20 (CH_2—CH_2—CH_2, m, 1H); 2.33 (CH_2—CH_2—CH_2, m, 1H); 2.60 (*cycle*, m, 2H); 2.71 (*cycle*, m, 2H); 2.91 (*cycle*, m, 2H); 3.01 (*cycle*, m, 6H); 3.03 (N—CH_2—P, 1H); 3.15 (*cycle*, m, 1H); 3.29 (*cycle*, m, 4H); 3.79 (*cycle*, m, 3H); 4.24 (N—CH_2—P, m, 1H); **^{13}C**{^{1}H} δ 19.5 (CH_2—CH_2—CH_2, s); 20.6 (CH_2—CH_2—CH_2, s); 33.7 (P—CH_2—P, dd, $^1J_{CP}$ = 115 Hz; $^1J_{CP}$ = 88 Hz); 42.3 (*cycle*, s,); 48.8 (*cycle*, s,); 50.0 (*cycle*, s); 50.1 (*cycle*, s); 52.3 (CH_2—N—CH_2—P, d, $^3J_{CP}$ = 7 Hz); 53.2 (*cycle*, s); 53.4 (N—CH_2—P, d, $^1J_{CP}$ = 87 Hz); 55.0 (*cycle*, s); 58.7 (*cycle*, s); 59.1 (*cycle*, s); 59.4 (*cycle*, s); **^{31}P**{^{1}H} δ 11.3 (HO—*P*—OH, m, 1P); 27.6 (*P*—CH_2—N, m, 1P).

MS: (+) 399.1 $[M+H^+]^+$; 421.0 $[M+Na^+]^+$; 437.2 $[M+K^+]^+$.

TLC (SiO_2, *i*PrOH–conc. aq. NH_4OH–H_2O 7:3:3): R_f = 0.2.

EA ($C_{14}H_{32}N_4O_5P_2 \cdot 1.5HCl \cdot 0.5H_2O$, M_R = 462.1): C 36.4 (36.2); H 7.5 (7.5); N 12.1 (12.0).

Example 35: *Synthesis of compound* ***30***



To a glass vial (4 mL), 1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (298 mg; 1.32 mmol; 4.5 equiv.) was added. Methylene-bis(phosphinic acid) (93.5 mg; 649 μmol; 2.2 equiv.), acetaldehyde (13.0 mg; 295 μmol; 1.0 equiv.) and aqueous HCl (6 M; 20 mL) were subsequently added and the resulting suspension was stirred 60 °C overnight. The mixture was then evaporated to dryness and several times co-evaporated with H_2O. The residue was purified by ion exchange chromatography (DOWEX 50; H^+-form; $H_2O \rightarrow$ 10 % aqueous pyridine). Pyridine fraction with product was evaporated to dryness and several times co-evaporated with H_2O. The residue was re-dissolved in H_2O (50 mL) and subsequently lyophilized. The final product was obtained as a white substance (62.3 mg; 51 %; 1 step; based on acetaldehyde).

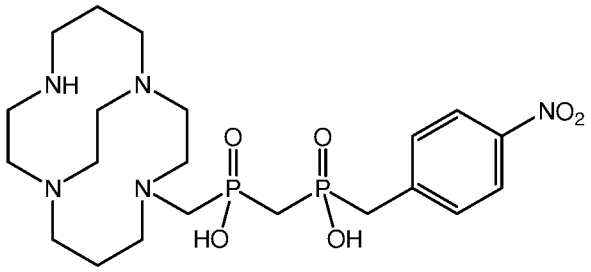
NMR (D_2O): **^{1}H** δ 1.19 (C*H*$_3$, dd, 3H, $^3J_{HP}$ = 15 Hz, $^2J_{HH}$ = 6 Hz); 1.72 (CH_2—C*H*$_2$—CH_2, dm, 1H, $^1J_{HH}$ = 16 Hz); 1.80 (CH_2—C*H*$_2$—CH_2, dm, 1H, $^1J_{HH}$ = 17 Hz); 2.15 (P—C*H*$_2$—P, t, 2H, $^2J_{HP}$ = 16 Hz); 2.27–2.39 (CH_2—C*H*$_2$—CH_2, m, 2H); 2.48 (*cycle*, m, 2H); 2.68 (*cycle*, m, 2H); 2.95–3.04 (*cycle*, m, 4H); 3.21–3.37 (*cycle*, bm, 11H) 3.51 (C*H*—CH_3, dq, 1H, $^2J_{HP}$ = 14 Hz, $^2J_{HH}$ = 6 Hz); 3.62 (*cycle*, m, 2H); 3.78 (*cycle*, m, 1H); 7.15 (P*H*, d, 1H, $^1J_{HP}$ = 533 Hz); **^{13}C**{^{1}H} 8.9 (*C*H$_3$, s); δ 22.1 (CH_2—*C*H$_2$—CH_2, s); 23.5 (CH_2—*C*H$_2$—CH_2, s); 36.7 (P—*C*H$_2$—P, dd, $^1J_{CP}$ = 81 Hz; $^1J_{CP}$ = 75 Hz); 41.6 (*cycle*, s); 46.2 (*cycle*, s); 49.7 (*cycle*, s); 50.9 (cycle, d, $^3J_{CP}$ = 6 Hz); 51.2 (*cycle*, s); 53.5 (N—*C*H$_2$—P, d, $^1J_{CP}$ = 92 Hz); 54.1 (*cycle*, s); 55.5 (*cycle*, s); 56.8 (*cycle*, s); 57.2 (*cycle*, s); 59.9 (*cycle*, s); **^{31}P** δ 19.8 (*P*H, dtm, 1P, $^1J_{PH}$ = 533 Hz, $^2J_{PH}$ = 16 Hz); 29.2 (*P*—CH_2—N, m, 1P).

MS: (−) 394.9 [M−H$^+$]$^-$. (+) 396.9 [M+H$^+$]$^+$; 419.0 [M+Na$^+$]$^+$; 441.0 [M−H$^+$+2Na$^+$]$^+$.

TLC (SiO_2, EtOH–conc. aq. NH_4OH 2:1): R_f = 0.7.

EA ($C_{15}H_{34}N_4O_4P_2 \cdot H_2O$, M_R = 414.2): C 43.5 (43.8); H 8.8 (8.5); N 13.5 (13.5).

Example 36: *Synthesis of compound* ***31***



To a glass vial (20 mL), 1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (1.12 g; 4.97 μmol; 1.6 equiv.) was added. Intermediate **B** (856 mg; 3.07 mmol; 1.0 equiv.), paraformaldehyde (92.4 mg; 3.08 mmol; 1.0 equiv.) and aqueous HCl (6 M; 15 mL) were subsequently added and the resulting suspension was stirred 80 °C overnight. The mixture was then evaporated to dryness and several times co-evaporated with H_2O. The residue was purified by ion exchange chromatography (DOWEX 50; H^+-form; $H_2O \rightarrow$ 10% aqueous pyridine). Pyridine fraction with product was evaporated to dryness and several times co-evaporated with H_2O. The crude product was purified by flash chromatography (C18; gradient elution H_2O—MeCN). Fractions with pure product were combined and evaporated to dryness. The residue was re-dissolved in H_2O (250 mL) and subsequently lyophilized. The final product was obtained as a white substance (1.04 g; 55 %; 1 step; based on intermediate **B**).

NMR (D_2O): **^{1}H** δ 1.69 (CH_2—C*H*$_2$—CH_2, m, 1H); 1.77 (CH_2—C*H*$_2$—CH_2, m, 1H); 2.10 (P—C*H*$_2$—P, m, 2H); 2.27 (CH_2—C*H*$_2$—CH_2, m, 1H); 2.39 (CH_2—C*H*$_2$—CH_2, m, 1H); 2.59 (*cycle*, m, 2H); 2.64 (*cycle*, m, 2H); 2.85–3.07 (*cycle*, m, 5H); 3.07–3.35 (*cycle*, P—C*H*$_2$—C, N—C*H*$_2$—P, m, 9H); 3.38 (*cycle*, m, 1H); 3.38 (*cycle*, m, 1H); 3.68 (*cycle*, m, 1H); 3.74–3.88 (*cycle*, N—C*H*$_2$—P, m, 3H); 7.51 (C*H*—C—CH_2, dd, 2H, $^2J_{HH}$ = 9 Hz, $^4J_{HP}$ = 2 Hz); 8.19 (C*H*—C—N, d, 2H, $^2J_{HH}$ = 9 Hz); **^{13}C**{^{1}H} δ 19.0 (CH_2—*C*H$_2$—CH_2, s); 20.2 (CH_2—*C*H$_2$—CH_2, s); 33.3 (P—*C*H$_2$—P, dd, $^1J_{CP}$ = 85 Hz, $^1J_{CP}$ = 82 Hz); 41.1 (P—*C*H$_2$—C, dd, $^1J_{CP}$ = 86 Hz, $^3J_{CP}$ = 3 Hz); 42.2 (*cycle*, s); 47.9 (*cycle*, s); 49.6 (*cycle*, s); 49.9 (*cycle*, s); 51.8 (*cycle*, d, $^3J_{CP}$ = 7 Hz); 54.1(*cycle*, s); 55.2 (P—*C*H$_2$—N, d, $^1J_{CP}$ = 90 Hz); 58.4 (*cycle*, s); 58.7 (*cycle*, s); 59.5 (*cycle*, s); 124.4 (*C*H—C—N, s); 131.3 (*C*H—C—CH_2, d, $^3J_{CP}$ = 5 Hz); 143.9 (CH—*C*—CH_2, d,

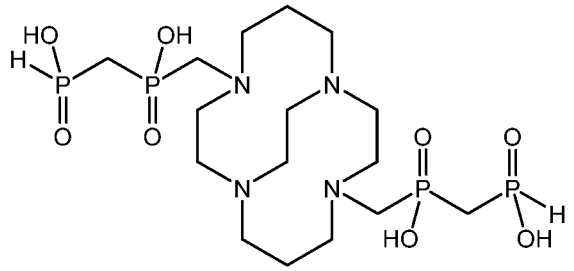
$^{2}J_{CP}$ = 8 Hz); 146.8 (CH—*C*—N, s); **^{31}P**{^{1}H} δ 23.3 (CH_2—*P*—CH_2, d, 1P, $^{2}J_{PP}$ = 11 Hz); 31.1 (CH_2—*P*—CH_2, d, 1P, $^{2}J_{PP}$ = 11 Hz).

MS: (−) 516.2 $[M-H^+]^-$.

TLC (SiO_2, EtOH–conc. aq. NH_4OH 4:1): R_f = 0.6.

EA ($C_{21}H_{37}N_5O_6P_2 \cdot 5.5H_2O$, M_R = 616.5): C 40.9 (40.8); H 7.9 (7.6); N 11.4 (11.7).

Example 37: *Synthesis of compound* ***32***



To a glass flask (25 mL), 1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (214 mg; 945 μmol; 1.0 equiv.) was added. Methylene-bis(phosphinic acid) (835 mg; 5.80 mmol; 5.5 equiv.), paraformaldehyde (63.5 mg; 2.12 mmol; 2.0 equiv.) and aqueous HCl (6 M; 5 mL) were subsequently added and the resulting suspension was stirred at 80 °C for two days. The mixture was then evaporated to dryness and several times co-evaporated with H_2O. The residue was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O). Fractions with product were joined and evaporated to dryness. The residue was re-dissolved in H_2O (200 mL) and subsequently lyophilized. The final product was obtained as a white substance (392 mg; 68 %; 1 step; based on 1,4,8,11-tetraazabicyclo[6.6.2]hexadecane).

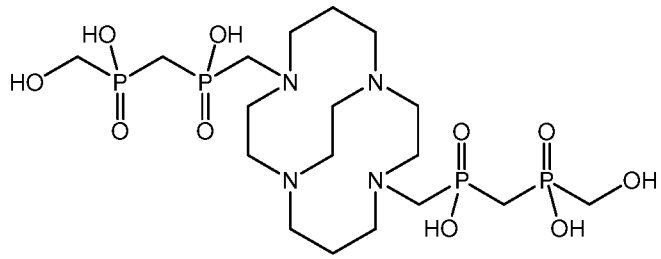
NMR (D_2O): **^{1}H** δ 1.67 (CH_2—C*H*$_2$—CH_2, bm, 2H); 1.82 (CH_2—C*H*$_2$—CH_2, bm, 2H); 1.99 (P—C*H*$_2$—P, t, 4H, $^{2}J_{HP}$ = 17 Hz); 2.78–3.19 (N—C*H*$_2$, bm, 20H); 3.26 (N—C*H*$_2$, bm, 2H); 3.62 (N—C*H*$_2$, bm, 2H); 7.14 (P*H*, d, 2H, $^{1}J_{HP}$ = 530 Hz); **^{13}C**{^{1}H} δ 24.4 (CH_2—*C*H_2—CH_2, s); 37.1 (P—*C*H_2—P, dd, $^{1}J_{CP}$ = 76 Hz, $^{1}J_{CP}$ = 72 Hz); 52.4 (*cycle*, s); 52.8 (*cycle*, s); 53.8 (*C*H_2—N—CH_2—P, d, $^{3}J_{CP}$ = 4 Hz); 53.8 (N—*C*H_2—P, d, $^{1}J_{CP}$ = 100 Hz); 56.5 (*cycle*, s); 57.1 (*cycle*, s); **^{31}P**{^{1}H} δ 19.8 (*P*H, dt, 2P, $^{1}J_{PH}$ = 530 Hz, $^{2}J_{PH}$ = 18 Hz); 32.5 (*P*—CH_2—N, t, 2P, $^{2}J_{PH}$ = 15 Hz).

MS: (−) 536.7 $[M-H^+]^-$.

TLC (SiO_2, *i*PrOH–conc. aq. NH_4OH–H_2O 7:3:3): R_f = 0.4.

EA ($C_{16}H_{38}N_4O_8P_4 \cdot 4H_2O$, M_R = 610.5): C 31.5 (31.3); H 7.6 (7.4); N 9.2 (9.2).

Example 38: *Synthesis of compound* ***33***



To a glass vial (4 mL), **32**·4H_2O (59.8 mg; 98 μmol; 1.0 equiv.) was added and it was followed by addition of paraformaldehyde (13.6 mg; 453 μmol; 4.6 equiv.) and aqueous HCl (6 M; 10 mL). The resulting suspension was stirred at 80 °C overnight. On the next day, the mixture was evaporated to dryness and several times co-evaporated with H_2O. The crude product was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O). Fractions with product were combined and evaporated to dryness. The residue was re-dissolved in H_2O (25 mL) and subsequently lyophilized. The final product was obtained as a white substance (51.3 mg; 80 %; 1 step; based on **32**·4H_2O).

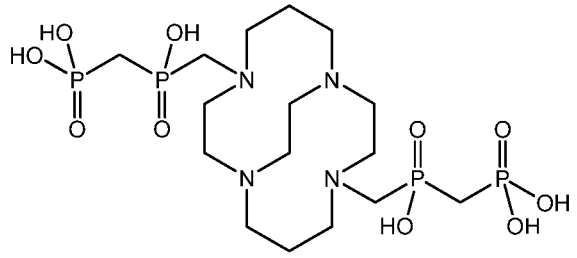
NMR (D_2O): **^{1}H** δ 1.82 (CH_2—CH_2—CH_2, m, 2H); 2.06 (CH_2—CH_2—CH_2, m, 2H); 2.30 (P—CH_2—P, t, 4H, $^2J_{HP}$ = 16 Hz); 2.67–3.63 (*cycle*, N—CH_2—P, bm, 24H); 3.67 (O—CH_2—P, d, 4H, $^2J_{HP}$ = 5 Hz); **^{13}C**{^{1}H} δ 22.1 (CH_2—CH_2—CH_2, s); 34.2 (P—CH_2—P, dd, $^1J_{CP}$ = 84 Hz, $^1J_{CP}$ = 73 Hz); 51.4 (*cycle*, s); 52.8 (*cycle*, s); 53.6 (CH_2—N—CH_2—P, d, $^3J_{CP}$ = 4 Hz); 54.9 (*cycle*, s); 55.2 (N—CH_2—P, d, $^1J_{CP}$ = 98 Hz); 57.8 (*cycle*, s); 61.3 (P—CH_2—O, d, $^3J_{CP}$ = 108 Hz) **^{31}P**{^{1}H} δ 27.6 (*P*—CH_2—N, bm, 2P); 40.6 (*P*—CH_2—O, m, 2P).

MS: (−) 596.8 $[M-H^+]^-$.

TLC (SiO_2, *i*PrOH–conc. aq. NH_4OH–H_2O 7:3:3): R_f = 0.5.

EA ($C_{18}H_{42}N_4O_{10}P_4$·3H_2O, M_R = 652.5): C 33.1 (33.4); H 7.4 (7.5); N 8.6 (8.3).

Example 39: *Synthesis of compound* ***34***



To a glass flask (20 mL), **32**·4H_2O (91.6 mg; 150 μmol; 1.0 equiv.) was added. Solution of $HgCl_2$ (173 mg; 638 μmol; 4.3 equiv.) in aqueous HCl (2 M; 5 mL) was added and the mixture was stirred at 60 °C for two days. Precipitate was filtered off and the mother liquor was saturated with H_2S. Precipitate was centrifuged off, washed with H_2O and the supernatant was evaporated to dryness. The residue was re-dissolved in aqueous HCl (3 %; 300 μL) followed by addition of excess of *i*PrOH (25 mL). On the next day, mother liquor was decanted off and the oily residue was several times co-evaporated with H_2O. The residue was re-dissolved in H_2O (100 mL) and subsequently lyophilized. Product was obtained as a white substance (68.4 mg; 68 %; 1 step, based on **32**·4H_2O).

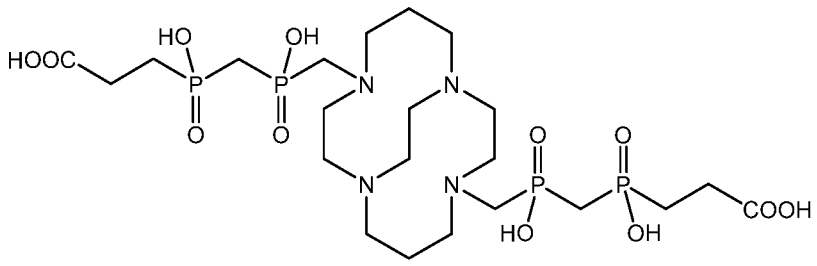
NMR (D_2O): **^{1}H** δ 1.68 (CH_2—C*H*$_2$—CH_2, bm, 2H); 1.81 (CH_2—C*H*$_2$—CH_2, bm, 2H); 1.92 (P—C*H*$_2$—P, t, 4H, $^2J_{HP}$ = 18 Hz); 2.75–3.21 (N—C*H*$_2$, bm, 20H); 3.27 (N—C*H*$_2$, bm, 2H); 3.66 (N—C*H*$_2$, bm, 2H); **^{13}C**{^{1}H} δ 24.5 (CH_2—*C*H_2—CH_2, s); 35.1 (P—*C*H_2—P, dd, $^1J_{CP}$ = 117 Hz, $^1J_{CP}$ = 75 Hz); 52.5 (*cycle*, s); 52.9 (*cycle*, s); 53.3 (N—*C*H_2—P, bm); 53.7 (*C*H_2—N—CH_2—P, bm); 56.7 (*cycle*, s); 57.0 (*cycle*, s); **^{31}P**{^{1}H} δ 12.4 (HO—*P*—OH, d, 2P, $^2J_{PP}$ = 7 Hz); 36.7 (*P*—CH_2—N, d, 2P, $^2J_{PP}$ = 7 Hz).

TLC (SiO_2, *i*PrOH–conc. aq. NH_4OH–H_2O 7:3:3): R_f = 0.1.

MS: (−) 569.2 $[M-H^+]^-$. (+) 571.4 $[M+H^+]^+$; 593.4 $[M+Na^+]^+$; 609.4 $[M+K^+]^+$.

EA ($C_{16}H_{38}N_4O_{10}P_4$·2.5HCl·H_2O, M_R = 679,6): C 28.3 (28.4); H 6.3 (6.2); N 8.2 (8.3).

Example 40: *Synthesis of compound* ***35***



To a glass vial (20 mL), 1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (148 mg; 653 μmol; 1.0 equiv.) was added. Intermediate **D** (688 mg; 3.18 mmol; 4.9 equiv.), paraformaldehyde (48.6 mg; 1.62 mmol; 2.5 equiv.) and aqueous HCl (12 M; 10 mL) were subsequently added and the resulting suspension was stirred at 80 °C for two days. The mixture was then evaporated to dryness and several times co-evaporated with H_2O. The residue was purified by column chromatography (SiO_2; EtOH–conc.

aq. NH_4OH 1:1; R_f = 0.4). Fractions with product were combined and evaporated to dryness. The residue was re-dissolved in H_2O (25 mL), treated with small amounts of charcoal and filtered through syringe microfilter (Millipore; 0.22 μm). The filtrate was further purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O). Fractions with product were combined and evaporated to dryness. The residue was re-dissolved in H_2O (125 mL) and subsequently lyophilized. The final product was obtained as a white substance (272 mg; 58 %; 1 step; based on 1,4,8,11-tetraazabicyclo[6.6.2]hexadecane).

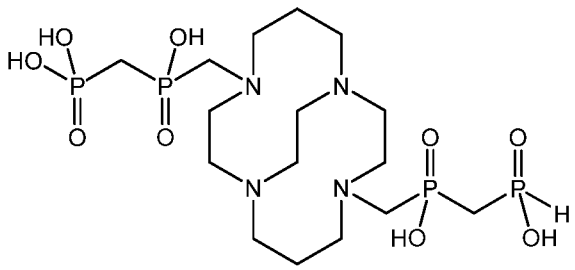
NMR (D_2O): ^{1}**H** δ 1.72 (CH_2—CH_2—CH_2, m, 2H); 1.74 (CH_2—CH_2—CH_2, m, 2H); 1.94 (P—CH_2—P, P—CH_2—C, m, 8H); 2.48 (CH_2—CO, t, 4H, $^3J_{HH}$ = 7 Hz); 2.92–3.31 (*cycle*, N—CH_2, bm, 22H); 3.52 (N—CH_2, bm, 2H); ^{13}**C**{^{1}H} δ 24.4 (CH_2—CH_2—CH_2, s); 26.8 (P—CH_2—C, d, $^1J_{CP}$ = 94 Hz); 31.0 (CH_2—CO, s); 34.9 (P—CH_2—P, dd, $^1J_{CP}$ = 76 Hz, $^1J_{CP}$ = 74 Hz); 52.4 (*cycle*, s); 52.8 (*cycle*, s); 54.2 (N—CH_2—P, d, $^1J_{CP}$ = 102 Hz); 54.4 (*cyclus*, d, $^3J_{CP}$ = 5 Hz); 57.1 (*cycle*, s); 57.3 (*cycle*, s); 182.8 (*C*O, d, $^3J_{CP}$ = 15 Hz); ^{31}**P**{^{1}H} δ 30.4 (CH_2—*P*—CH_2, d, 2P, $^2J_{PP}$ = 10 Hz); 33.7 (CH_2—*P*—CH_2, d, 2P, $^2J_{PP}$ = 10 Hz).

MS: (−) 663.3 $[M-H_3O^+]^-$; 681.3 $[M-H^+]^-$. (+) 683.2 $[M+H^+]^+$; 727.2 $[M-H^+ +2Na^+]^+$.

TLC (SiO_2, EtOH–conc. NH_4OH 1:1): R_f = 0.3.

EA ($C_{22}H_{46}N_4O_{12}P_4 \cdot 2H_2O$, M_R = 718.6): C 36.8 (36.9); H 7.0 (7.3); N 7.8 (7.5).

Example 41: *Synthesis of compound* ***36***



To a glass vial (4 mL), **29**·1.5HCl·0.5H_2O (51.3 mg; 111 μmol; 1.0 equiv.) was added. Methylene-bis(phosphinic acid) (59.2 mg; 411 μmol; 3.7 equiv.), paraformaldehyde (4.9 mg; 163 μmol; 1.5 equiv.) and aqueous HCl (12 M; 1 mL) were subsequently added and the resulting suspension was stirred at 80 °C for two days. The mixture was then evaporated to dryness and several times co-evaporated with H_2O. The residue was purified by ion exchange chromatography (DOWEX 50;

H^+-form; H_2O). Fractions with product were combined and evaporated to dryness. The residue was dried in vacuum pump and subsequently in vacuum desiccator over P_2O_5. Resulting product was obtained as a white substance (35.0 mg; 55 %; 1 step; based on **29**·1.5HCl·0.5H_2O).

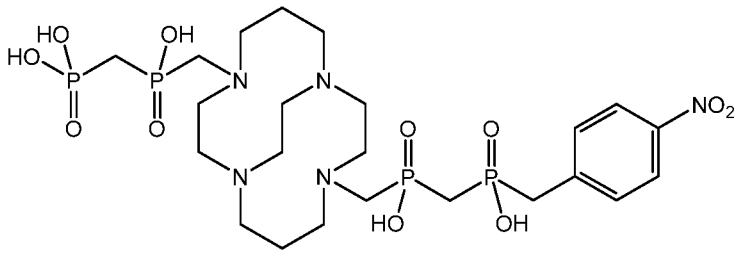
NMR (D_2O): **^{1}H** δ 1.83–2.11 (CH_2—CH_2—CH_2, bm, 4H); 2.24 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 15 Hz); 2.37 (CH_2—CH_2—CH_2, dd, 2H, $^2J_{HP}$ = 18 Hz, $^2J_{HP}$ = 16 Hz); 2.64–3.44 (*cycle*, N—CH_2—P, bm, 24H); **^{13}C**{^{1}H} δ 22.2 (CH_2—CH_2—CH_2, s); 23.7 (CH_2—CH_2—CH_2, s); 34.2 (P—CH_2—P, dd, $^1J_{CP}$ = 122 Hz, $^1J_{CP}$ = 82 Hz); 36.3 (P—CH_2—P, t, $^1J_{CP}$ = 82 Hz); 49.3–57.4 (12 × N—CH_2, bm); **^{31}P** δ 19.0 (HO—*P*—OH, m, 1P); 24.3 (*P*H, dm, 1P, $^1J_{PH}$ = 533 Hz); 26.7 (*P*—CH_2—N, bm, 1P); 27.8 (*P*—CH_2—N, bm, 1P).

MS: (−) 553.1 $[M-H^+]^-$. (+) 555.2 $[M+H^+]^+$; 577.2 $[M+Na^+]^+$.

TLC (SiO_2, EtOH–conc. aq. NH_4OH 1:1): R_f = 0.3.

EA ($C_{16}H_{38}N_4O_9P_4·H_2O$, M_R = 572.4): C 33.6 (33.4); H 7.0 (6.7); N 9.8 (9.9).

Example 42: *Synthesis of compound* ***37***



To a glass vial (4 mL), **29**·1.5HCl·0.5H_2O (403 mg; 872 μmol; 1.0 equiv.) was added. Intermediate **B** (294 mg; 1.05 mmol; 1.2 equiv.), paraformaldehyde (39.3 mg; 1.33 mmol; 1.5 equiv.) and aqueous HCl (12 M; 5 mL) were subsequently added and the resulting suspension was stirred at 80 °C for three days. The mixture was then evaporated to dryness and several times co-evaporated with H_2O. The residue was purified was purified by flash chromatography (C18; gradient elution H_2O–0.1% TFA–MeCN). Fractions with pure product were combined and evaporated to dryness. The residue was re-dissolved in H_2O (250 mL) and subsequently lyophilized. Resulting product was obtained as a yellow substance (417 mg; 62 %; 1 step; based on **29**·1.5HCl·0.5H_2O).

NMR (D_2O): **^{1}H** δ 2.02 (CH_2—CH_2—CH_2, bm, 2H); 2.32 (CH_2—CH_2—CH_2, bm, 2H); 2.40 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 16 Hz); 2.48 (P—CH_2—P, dd, 2H, $^2J_{HP}$ = 20 Hz,

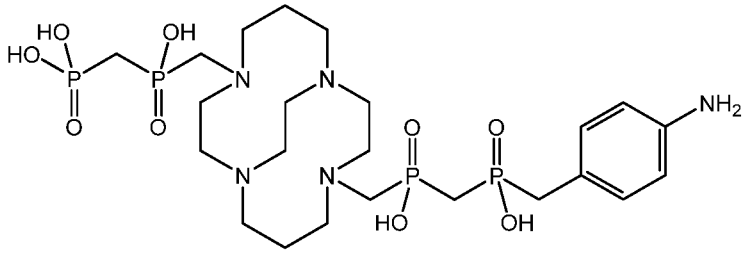
$^{2}J_{HP}$ = 17 Hz); 2.79–3.98 (*cycle*, N—CH_2—P, P—CH_2—C, bm, 26H); 7.57 (C*H*, dd, 2H, $^{3}J_{HH}$ = 9 Hz, $^{4}J_{HP}$ = 2 Hz); 8.24 (C*H*, d, 2H, $^{3}J_{HH}$ = 9 Hz); **^{13}C**{^{1}H} δ 20.5 (CH$_2$—*C*H$_2$—CH$_2$, s); 21.0 (CH$_2$—*C*H$_2$—CH$_2$, s); 32.2 (P—*C*H$_2$—P, dd, $^{1}J_{CP}$ = 124 Hz, $^{1}J_{CP}$ = 84 Hz); 33.2 (P—*C*H$_2$—P, t, $^{1}J_{CP}$ = 82 Hz); 39.3 (P—*C*H$_2$—C, d, $^{1}J_{CP}$ = 89 Hz); 48.0–59.6 (12 × N—*C*H$_2$, bm); 124.5 (*C*H—C—N, d, $^{4}J_{CP}$ = 3 Hz); 131.5 (*C*H—C—CH$_2$, d, $^{3}J_{CP}$ = 6 Hz); 141.8 (CH—*C*—CH$_2$, d, $^{2}J_{CP}$ = 9 Hz); 147.2 (CH—*C*—N, s); **^{31}P**{^{1}H} δ 18.0 (HO—*P*—OH, m, 1P); 24.0 (*P*—CH$_2$—N, bm, 1P); 25.6 (*P*—CH$_2$—N, bm, 1P); 39.0 (*P*—CH$_2$—C, m, 1P).

MS: (−) 687.8 [M−H$^+$]$^-$; 709.7 [M−2H$^+$+Na$^+$]$^-$; 725.7 [M−2H$^+$+K$^+$]$^-$. (+) 689.9 [M+H$^+$]$^+$; 711.9 [M+Na$^+$]$^+$; 727.8 [M+K$^+$]$^+$; 749.8 [M−H$^+$+Na$^+$+K$^+$]$^+$.

TLC (SiO$_2$, *i*PrOH–conc. aq. NH$_4$OH–H$_2$O 7:3:3): R_f = 0.3.

EA (C$_{23}$H$_{43}$N$_5$O$_{11}$P$_4$·4.5H$_2$O, M_R = 770.6): C 28.3 (28.4); H 6.3 (6.2); N 8.2 (8.3).

Example 43: *Synthesis of compound* ***38***



In a glass flask (250 ml), **37**·4.5H$_2$O (288 mg; 374 μmol) was dissolved in H$_2$O (100 mL) and the resulting mixture was briefly washed with gaseous argon. Pd@C catalyst (10 %; 44 mg) was subsequently added and the resulting suspension was then treated with gaseous H$_2$ at 60 °C overnight. The catalyst was then filtered off and the filtrate was evaporated to dryness. The residue was re-dissolved in H$_2$O (250 mL) and subsequently lyophilized. Resulting product was obtained as a yellowish substance (257 mg; 94 %; 1 step; based on **37**·4.5H$_2$O).

NMR (D$_2$O): **^{1}H** δ 1.80 (CH$_2$—C*H*$_2$—CH$_2$, bm, 2H); 1.86 (CH$_2$—C*H*$_2$—CH$_2$, bm, 2H); 2.10 (P—C*H*$_2$—P, m, 2H); 2.21 (P—C*H*$_2$—P, m, 2H); 2.65–3.77 (*cycle*, N—C*H*$_2$—P, P—C*H*$_2$—C, bm, 26H); 6.97 (C*H*, d, 2H, $^{3}J_{HH}$ = 8 Hz); 7.25 (C*H*, d, 2H, $^{3}J_{HH}$ = 8 Hz); **^{13}C**{^{1}H} δ 20.1 (CH$_2$—*C*H$_2$—CH$_2$, s); 20.5 (CH$_2$—*C*H$_2$—CH$_2$, s); 32.7 (P—*C*H$_2$—P, m); 33.4 (P—*C*H$_2$—P, m; 33.6 (P—*C*H$_2$—C, d, $^{1}J_{CP}$ = 91 Hz); 46.7–57.2 (12 × N—*C*H$_2$, bm); 123.0 (CH—*C*—N, s); 118.2 (*C*H—C—N, m); 130.8 (*C*H—C—CH$_2$,

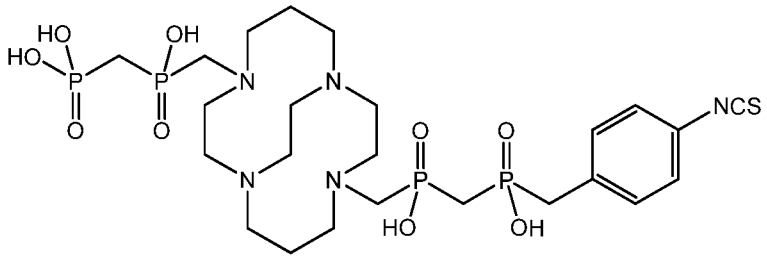
d, $^{3}J_{CP}$ = 5 Hz); 140.3 (CH—*C*—CH_2, m); **^{31}P**{^{1}H} δ 13.5 (HO—*P*—OH, bm, 1P); 24.6 (*P*—CH_2—N, bm, 1P); 23.6 (*P*—CH_2—N, bm, 1P); 32.6 (*P*—CH_2—C, bm, 1P).

MS: (−) 658.0 $[M-H^+]^-$; 679.9 $[M-2H^+ + Na^+]^-$. (+) 659.9 $[M+H^+]^+$; 981.9 $[M+Na^+]^+$; 697.8 $[M+K^+]^+$.

TLC (SiO_2, *i*PrOH–conc. aq. NH_4OH–H_2O 7:3:3): R_f = 0.3.

EA ($C_{23}H_{45}N_5O_9P_4 \cdot 4H_2O$, M_R = 731.6): C 37.8 (37.6); H 7.3 (7.2); N 9.6 (9.5).

Example 44: *Synthesis of compound* ***39***



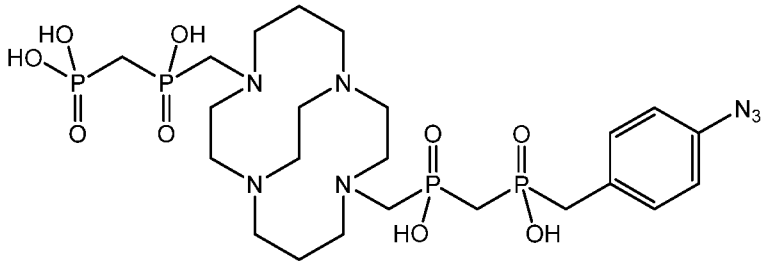
In a glass flask (100 mL), **38**·$4H_2O$ (48.3 mg; 66,0 μmol, 1.0 equiv.) was dissolved in H_2O (20 mL). Freshly prepared solution of $CSCl_2$ (15 mM; 20 mL; 300 μmol; 4.5 equiv.) in CCl_4 was then added and the resulting biphasic mixture was vigorously stirred at room temperature overnight. The organic layer was separated off and the aqueous layer was evaporated to dryness. The crude product was purified by preparative HPLC (C8; gradient elution H_2O–0.1% TFA–MeCN). Fraction with product was directly lyophilized. Product was obtained as a white substance (35.2 mg; 67 %; 1 step; based on **38**·$4H_2O$).

NMR (D_2O): **^{1}H** δ 2.02 (CH_2—C*H*$_2$—CH_2, bm, 2H); 2.29 (P—C*H*$_2$—P, t, 2H, $^{2}J_{HP}$ = 16 Hz); 2.32 (CH_2—C*H*$_2$—CH_2, bm, 2H); 2.37 (P—C*H*$_2$—P, t, 2H, $^{2}J_{HP}$ = 19 Hz); 2.86–3.92 (*cycle*, N—C*H*$_2$—P, P—C*H*$_2$—C, bm, 26H); 7.37 (C*H*, d, 2H, $^{3}J_{HH}$ = 8 Hz); 7.39 (C*H*, m, 2H); **^{13}C**{^{1}H} 20.8 (CH_2—*C*H_2—CH_2, s); 21.3 (CH_2—*C*H_2—CH_2, s); 31.7 (P—*C*H_2—P, dd, $^{1}J_{CP}$ = 120 Hz, $^{1}J_{CP}$ = 83 Hz); 32.3 (P—*C*H_2—P, t, $^{1}J_{CP}$ = 82 Hz); 38.4 (P—*C*H_2—C, d, $^{1}J_{CP}$ = 91 Hz); 46.6–59.1 (12 × N—*C*H_2, bm); 126.7 (*C*H—C—N, s); 130.1 (CH—*C*—N, s); 131.8 (*C*H—C—CH_2, s); 132.2 (CH—*C*—CH_2, d, $^{2}J_{CP}$ = 8 Hz); 134.8 (*C*S, s); **^{31}P**{^{1}H} δ 16.3 (HO—*P*—OH, m, 1P); 23.4 (*P*—CH_2—N, bm, 1P); 23.6 (*P*—CH_2—N, bm, 1P); 38.3 (*P*—CH_2—C, m, 1P).

MS: (−) 699.6 $[M-H^+]^-$; 721.6 $[M-2H^+ + Na^+]^-$; 737.6 $[M-2H^+ + K^+]^-$. (+) 701.8 $[M+H^+]^+$; 723.8 $[M+Na^+]^+$; 739.8 $[M+K^+]^+$.

EA ($C_{24}H_{43}N_5O_9P_4S \cdot 3.5H_2O$, M_R = 796.1): C 36.2 (36.2); H 6.3 (6.3); N 8.8 (8.7).

Example 45: *Synthesis of compound* ***40***



In a glass vial (4 mL), **37**·4H_2O (161 mg; 220 μmol; 1.0 equiv.) was dissolved in aqueous HCl (243.8 mM; 1800 μL; 440 μmol; 2.0 equiv.) and the resulting mixture was cooled in an ice bath (1 °C). Freshly prepared aqueous solution of $NaNO_2$ was then gradually added (290 mM; 1.0 mL; 290 μmol; 1.3 equiv.; 100 μL each three minutes). Freshly prepared aqueous solution of NaN_3 (580 mM; 760 μL; 441 μmol; 2.0 equiv.) was then added. The reaction mixture was then stirred at room temperature for three hours. The crude product was divided into two halves which were successively purified by preparative HPLC (C8; gradient elution H_2O–0.1% TFA–MeCN). Fraction with product were combined and directly lyophilized. Product was obtained as a white substance (29.5 mg; 57 %; 1 step; based on **37**·4H_2O).

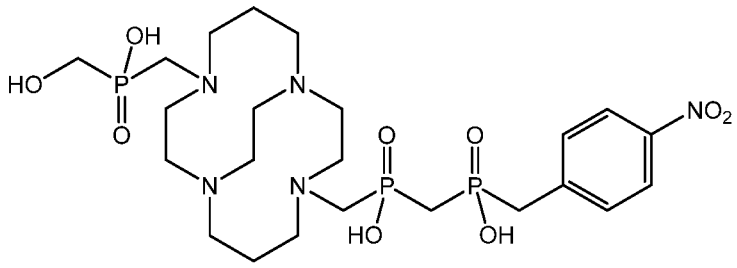
NMR (D_2O): ^{1}**H** δ 2.07 (CH_2—CH_2—CH_2, m, 2H); 2.18 (CH_2—CH_2—CH_2, m); 2.28–2.41 (P—CH_2—P, m, 4H); 2.70–3.82 (*cycle*, N—CH_2—P, P—CH_2—C, bm, 26H); 7.17 (C*H*—C—N, d, 2H, $^{3}J_{HH}$ = 7 Hz); 7.31 (C*H*—C—CH_2, dd, 2H, $^{3}J_{HH}$ = 7 Hz, $^{H}J_{HP}$ = 2 Hz); ^{13}**C**{^{1}H} δ 20.5 (CH_2—CH_2—CH_2, s); 22,5 (CH_2—CH_2—CH_2, s); 32.2 (P—CH_2—P, dd, $^{1}J_{CP}$ = 121 Hz, $^{1}J_{CP}$ = 82 Hz); 32.3 (P—CH_2—P, dd, $^{1}J_{CP}$ = 82 Hz); 36.6 (P—CH_2—C, d, $^{1}J_{CP}$ = 93 Hz); 47.2–60.1 (12 × N—CH_2, bm); 123.5 (C*H*—C—N, s); 131.7 (C*H*—C—CH_2, d, $^{3}J_{CP}$ = 4 Hz); 132.2 (CH—C—CH_2, d, $^{2}J_{CP}$ = 7 Hz); 141.0 (CH—C—N, s); ^{31}**P**{^{1}H} δ 17.5 (HO—P—OH, m, 1P); 22.2 (P—CH_2—N, bm, 1P); 24.0 (P—CH_2—N, bm, 1P); 36.8 (P—CH_2—C, m, 1P).

MS: (−) 666.0 [M−H_3O^+]$^-$; 684.1 [M−H^+]$^-$. (+) 688.1 [M+H^+]$^+$; 708.1 [M+Na^+]$^+$; 724.0 [M+K^+]$^+$; 730.1 [M−H^++2Na^+]$^+$.

TLC (SiO_2, EtOH–conc. aq. NH_4OH 1:1): R_f = 0.2.

EA ($C_{23}H_{43}N_7O_9P_4$·3H_2O, M_R = 739.6): C 37.4 (37.2); H 6.7 (6.6); N 13.3 (13.3).

Example 46: *Synthesis of compound* ***41***



To a glass vial (20 mL), **31**·5.5H_2O (50.9 mg; 82.6 μmol; 1.0 equiv.) was added. Paraformaldehyde (10.1 mg; 343 μmol; 4.2 equiv.), and hydroxymethylphosphinic acid (50.8 mg; 529 μmol; 6.4 equiv.), and aqueous HCl (6 M; 2 mL) were subsequently added and the resulting suspension was stirred at 80 °C overnight. The mixture was then evaporated to dryness and several times co-evaporated with H_2O. The residue was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O). Fractions with product were combined, evaporated to dryness and several times co-evaporated with H_2O. The crude product was purified by preparative HPLC (C8; gradient elution H_2O–0,1% TFA–MeCN). Fraction with product was directly lyophilized. Resulting product was obtained as a yellowish substance (25.8 mg; 46 %; 1 step; based on **31**·5.5H_2O).

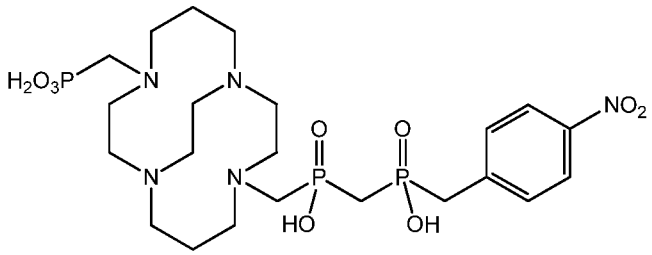
NMR (D_2O): **^{1}H** δ 1.84 (CH_2—CH_2—CH_2, m, 2H); 2.15–2.55 (CH_2—CH_2—CH_2, P—CH_2—P, m, 4H); 2.76 (*cycle*, m, 4H); 2.98 (*cycle*, m, 2H); 3.09 (*cycle*, m, 2H); 3.18–3.84 (*cycle*, N—CH_2—P, P—CH_2—C, O—CH_2—P, m, 20H); 7.57 (C*H*—C—CH_2, d, 2H, $^2J_{HH}$ = 8 Hz,); 8.25 (C*H*—C—N, d, 2H, $^2J_{HH}$ = 8 Hz); **^{13}C**{^{1}H} δ 20.7 (CH_2—*C*H_2—CH_2, s); 33.5 (P—*C*H_2—P, t, $^1J_{CP}$ = 81 Hz); 39.5 (P—*C*H_2—C, dd, $^1J_{CP}$ = 88 Hz); 49.1 (*cycle*, s); 49.2 (*cycle*, s); 50.2 (*cycle*, s); 51.7 (P—*C*H_2—N, d, $^1J_{CP}$ = 84 Hz); 54.6 (*cycle*, s); 54.9 (*cycle*, s); 58.3 (*cycle*, s); 58.9 (P—*C*H_2—N, d, $^1J_{CP}$ = 83 Hz); 58.9 (P—*C*H_2—O, d, $^1J_{CP}$ = 116 Hz); 124.6 (*C*H—C—N, s); 131.6 (*C*H—C—CH_2, d, $^3J_{CP}$ = 5 Hz); 142.3 (CH—*C*—CH_2, d, $^2J_{CP}$ = 8 Hz); 147.2 (CH—*C*—N, s); **^{31}P**{^{1}H} δ 23.6 (*P*—CH_2—*P*, bm, 1P); 29.7 (*P*—CH_2—*P*, bm, 1P); 37.3 (*P*—CH_2—O, m, 1P).

MS: (−) 623.5 [M−H^+]$^-$. (+) 625.4 [M+H^+]$^+$; 647.7 [M+Na^+]$^+$; 663.5 [M+K^+]$^+$.

TLC (SiO_2, EtOH–conc. aq. NH_4OH 2:1): R_f = 0.6.

EA ($C_{23}H_{42}N_5O_9P_3$·3H_2O, M_R = 679.6): C 40.7 (40.6); H 7.1 (7.1); N 10.3 (10.5).

Example 47: *Synthesis of compound* ***42***



To a glass vial (20 mL), **31**·5.5H_2O (336 mg; 545 μmol; 1.0 equiv.) was added. Paraformaldehyde (44.2 mg; 1.47 mmol; 2.7 equiv.), and phosphorous acid (380 mg; 4.63 mmol; 8.5 equiv.), and aqueous HCl (12 M; 10 mL) were subsequently added and the resulting suspension was stirred at 40 °C for four days. The mixture was then evaporated to dryness and several times co-evaporated with H_2O. The residue was purified by ion exchange chromatography (DOWEX 50; H^+-form; H_2O). Fractions with product were combined, evaporated to dryness and several times co-evaporated with H_2O. The crude product was purified by flash chromatography (C18; gradient elution H_2O–0.1% TFA–MeCN). Fraction with product was directly lyophilized. Resulting product was obtained as a yellow substance (194 mg; 54 %; 1 step; based on **31**·5.5H_2O).

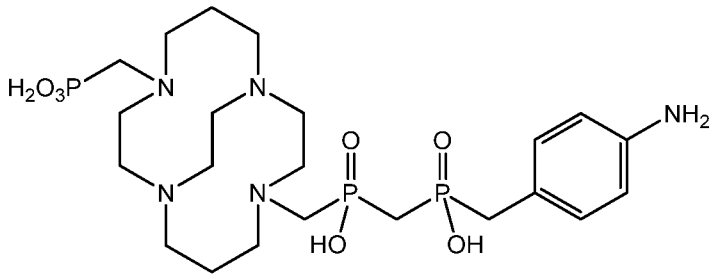
NMR (D_2O): ^{1}**H** δ 1.85 (CH_2—CH_2—CH_2, m, 2H); 2.12 (CH_2—CH_2—CH_2, m, 1H); 2.27 (P—CH_2—P, m, 4H); 2.35 (CH_2—CH_2—CH_2, m, 1H); 2.66–2.72 (*cycle*, m, 3H); 2.89 (*cycle*, m, 2H); 2.98–3.12 (*cycle*, m, 3H); 3.14–3.60 (*cycle*, N—CH_2—P, P—CH_2—C, m, 18H); 7.42 (C*H*—C—CH_2, d, 2H, $^2J_{HH}$ = 8 Hz,); 8.20 (C*H*—C—N, d, 2H, $^2J_{HH}$ = 8 Hz); ^{31}**P**{^{1}H} δ 21.2 (HO—*P*—OH, s, 1P); 23.6 (*P*—CH_2—*P*, d, 1P, $^2J_{PP}$ = 8 Hz); 29.7 (*P*—CH_2—*P*, d, 1P, $^2J_{PP}$ = 8 Hz).

MS: (−) 609.9 $[M-H^+]^-$. (+) 612.1 $[M+H^+]^+$; 634.2 $[M+Na^+]^+$; 650.2 $[M+K^+]^+$.

TLC (SiO_2, EtOH–conc. aq. NH_4OH 2:1): R_f = 0.4.

EA ($C_{22}H_{40}N_5O_9P_3$·2.5H_2O, M_R = 656.5): C 40.3 (40.5); H 6.9 (7.0); N 10.7 (10.4).

Example 48: *Synthesis of compound* ***43***



In a glass flask (100 mL), **42**·2.5H_2O (185 mg; 0.28 mmol; 1.0 equiv.) was dissolved in H_2O (10 ml) and the flask was briefly washed with gaseous argon. Catalyst (10 % Pd@C; 54 mg) was then added and the resulting suspension was saturated with gaseous H_2 at 60 °C overnight. The catalyst was then filtered off and the filtrate was evaporated to dryness. The residue was re-dissolved in H_2O (200 mL) and subsequently lyophilized. Resulting product was obtained as a white substance (158 mg; 89 %; 1 step; based on **42**·2.5H_2O).

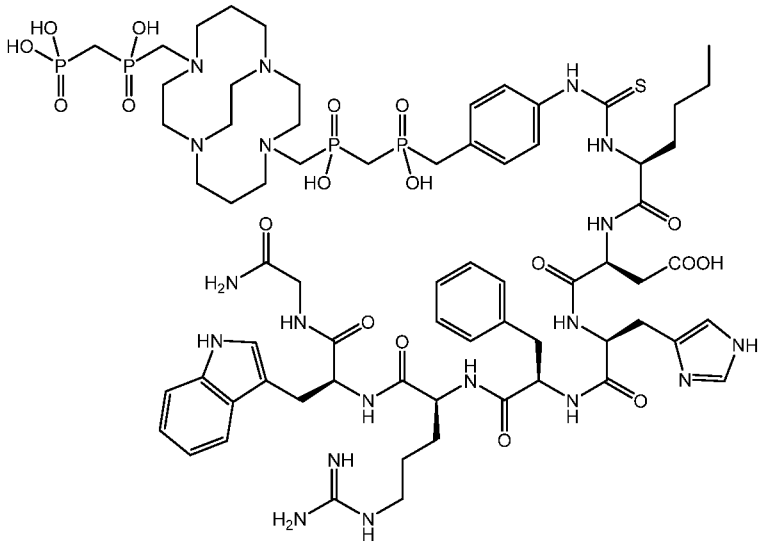
NMR (D_2O): **^{1}H** δ 1.77 (CH_2—CH_2—CH_2, m, 1H); 1.87 (CH_2—CH_2—CH_2, m, 1H); 2.12 (CH_2—CH_2—CH_2, m, 1H); 2.22–2.40 (CH_2—CH_2—CH_2, P—CH_2—P, bm, 5H); 2.62–2.79 (*cycle*, m, 2H); 2.91–3.02 (*cycle*, m, 4H); 3.07–3.48 (*cycle*, N—CH_2—P, P—CH_2—C, m, 20H); 6.89 (C*H*—C—N, d, 2H, $^2J_{HH}$ = 8 Hz); 7.33 (C*H*—C—CH_2, d, 2H, $^2J_{HH}$ = 8 Hz,); **^{13}C**{^{1}H} δ 18.9 (CH_2—*C*H_2—CH_2, s); 22.3 (CH_2—*C*H_2—CH_2, s); 34.1 (P—*C*H_2—P, t, $^1J_{CP}$ = 83 Hz); 37.5 (P—*C*H_2—C, d, $^1J_{CP}$ = 90 Hz); 41.2–59.5 (12 × N—*C*H_2, bm); 120.1 (CH—*C*—N, s); 127.1 (*C*H—C—N, m); 129.3 (*C*H—C—CH_2, d, $^3J_{CP}$ = 5 Hz); 134.5 (CH—*C*—CH_2, m); **^{31}P**{^{1}H} δ 19.3 (HO—*P*—OH, m, 1P); 22.4 (*P*—CH_2—*P*, d, 1P, $^2J_{PP}$ = 9 Hz); 31.5 (*P*—CH_2—*P*, bm, 1P).

MS: (−) 580.2 $[M-H^+]^-$. (+) 582.8 $[M+H^+]^+$; 603.2 $[M+Na^+]^+$; 619.8 $[M+K^+]^+$.

TLC (SiO_2, EtOH–conc. aq. NH_4OH 2:1): R_f = 0.3.

EA ($C_{22}H_{42}N_5O_7P_3$·3H_2O, M_R = 635.6): C 41.2 (41.6); H 6.8 (6.6); N 10.7 (11.0).

Example 49: *Synthesis of targeting conjugate* ***44***



To a glass vial (4 mL), **39**·3.5H_2O (5.3 mg; 6.7 μmol; 1.1 equiv.) was added. Peptide HNleAspHis^D-PheArgTrpGlyNH$_2$ (5.9 mg; 6.4 μmol; 1.0 equiv.), aqueous

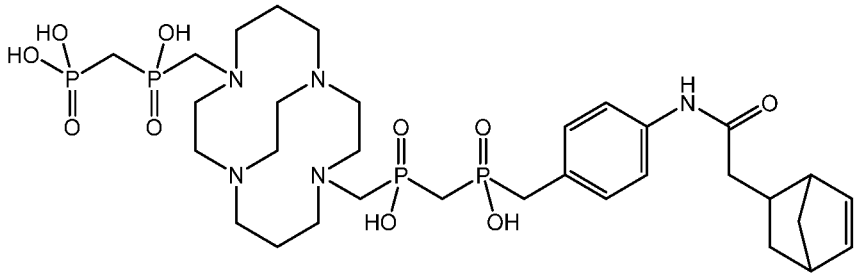
buffer H_3BO_3–LiOH (750 mM v D_2O; pD = 10.1; 400 µL; 300 µmol; 50 equiv.) and H_2O (600 µL) were then added and the resulting mixture was stirred at room temperature overnight. The crude product was purified by preparative HPLC (C8; gradient elution H_2O–0.1% TFA–MeCN). Fraction with product was lyophilized. Resulting product was obtained as a white substance (5.7 mg; 55 %; 1 step; based on **39**·3.5H_2O).

NMR (D_2O): **^{1}H** δ 0.86 (C*H*$_3$, t, 3H, $^3J_{HH}$ = 7 Hz); 1.01–1.53 (C*H*$_2$, bm, 10H); 1.68–2.29 (C*H*$_2$, P—C*H*$_2$—P, *cycle*, bm, 8 H); 2.47–3.73 (*cycle*, C*H*$_2$, P—C*H*$_2$—N, P—C*H*$_2$—C, bm, 36H); 3.80 (C*H*$_2$, m, 2H); 4.11 (C*H*, m, 1H); 4.45 (C*H*, m, 1H); 4.51 (C*H*, m, 1H); 4.55 (C*H*, m, 1H); 4.59 (C*H*, m, 1H); 4.69 (C*H*, m, 1H); 6.90 (CH$_2$—C—C*H*—N, s, 1H); 7.14 (C*H*, t, 1H, $^3J_{HH}$ = 7 Hz); 7.14–7.27 (*arom.*, m, 6H); 7.29–7.38 (*arom.*, m, 5H); 7.46 (C*H*, d, 1H, $^3J_{HH}$ = 8 Hz); 7.66 (C*H*, d, 1H, $^3J_{HH}$ = 8 Hz); 8.03 (N—C*H*—N, s, 1H); **^{31}P**{^{1}H} δ 13.2 (HO—*P*—OH, bm, 1P); 25.3 (*P*—CH$_2$—N, bm, 1P); 27.4 (*P*—CH$_2$—N, bm, 1P); 32.3 (*P*—CH$_2$—C, bm, 1P).

MS: (−) 1628.2 $[M-H^+]^-$. (+) 1630.4 $[M+H^+]^+$.

TLC (SiO_2, EtOH–conc. aq. NH_4OH 1:1): R_f = 0.2.

Example 50: *Synthesis of conjugate* ***45***



In a glass vial (4 mL), **38**·4H_2O (5.3 mg; 6.7 µmol; 1.1 equiv.) and *N*-hydroxysuccinimidester of 5-norbornen-2-acetic acid (21.1 mg; 84.6 µmol; 2.2 equiv.) were dissolved in a mixture of aqueous buffer H_3PO_4–NaOH (1.0 M pH = 8.1; 1.00 mL; 1.0 mmol; 26 equiv.) and MeCN (0.5 mL). The resulting mixture was stirred at room temperature overnight. The crude product was purified by preparative HPLC (C8; gradient elution H_2O–0.1% TFA–MeCN). Fraction with product was lyophilized. Resulting product was obtained as a white substance (26.1 mg; 71 %; 1 step; based on **38**·4H_2O).

NMR (D_2O): **^{1}H** δ 1.41–1.56 (CH—C*H*$_2$—CH, C*H*$_2$ bm, 2H); 1.62–1.75 (C*H*$_2$, CH—C*H*$_2$—CH, bm, 2H); 1.94–2.32 (P—C*H*$_2$—P, *cycle*, bm, 6H); 2.44 (P—C*H*$_2$—P, t, 2H,

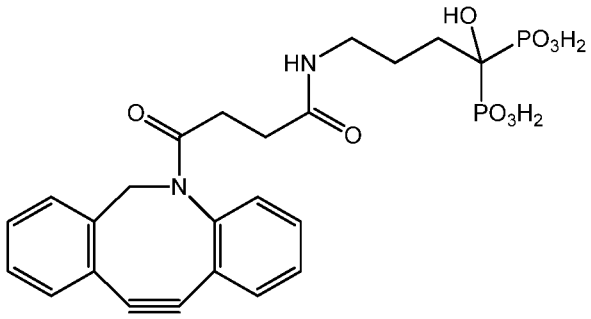
$^{2}J_{HP}$ = 17 Hz); 2.84–4.16 (*cycle*, *CH*, N—C*H*$_2$—P, P—C*H*$_2$—C, bm, 31H); 5.96 (C*H*, dd, $^{3}J_{HH}$ = 12 Hz, $^{3}J_{HH}$ = 5 Hz); 6.32 (C*H*, dd, $^{3}J_{HH}$ = 12 Hz, $^{3}J_{HH}$ = 6 Hz); 6.98 (C*H*, d, 2H, $^{3}J_{HH}$ = 8 Hz); 7.63 (C*H*, d, 2H, $^{3}J_{HH}$ = 8 Hz); **^{31}P**{^{1}H} δ 21.1 (HO—*P*—OH, bm, 1P); 23.5 (*P*—CH$_2$—N, bm, 1P); 24.9 (*P*—CH$_2$—N, bm, 1P); 29.3 (*P*—CH$_2$—C, bm, 1P).

MS: (–) 792.5 [M–H$^+$]$^-$.

TLC (SiO$_2$, EtOH–conc. aq. NH$_4$OH 1:1): R_f = 0.3.

EA ($C_{32}H_{55}N_5O_{10}P_4$·TFA·2H$_2$O, M_R = 943.3): C 43.3 (43.4); H 6.4 (6.2); N 7.4 (7.7).

Example 51: *Synthesis of intermediate product* ***F***



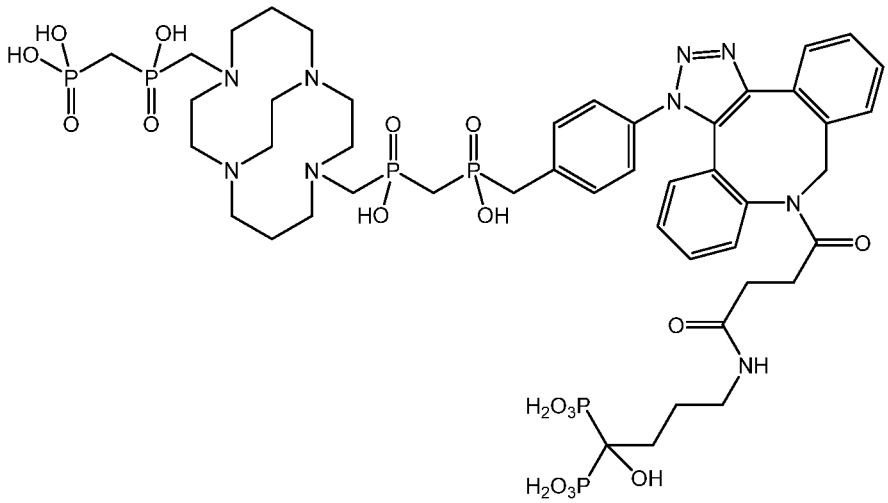
In a glass vial (4 mL), sodium aldendronate trihydrate (21.0 mg; 64.6 μmol; 1.4 equiv.) was dissolved in aqueous NaOH (250.6 mM; 773 μL; 194 μmol; 4.2 equiv.) and the resulting mixture was cooled in an ice bath (5 °C). Solution of *N*-hydroxysuccinimidester of 4-dibenzocyclooctynamidobutanoic acid (18.4 mg; 45.7 μmol; 1.0 equiv.) in dry DMSO (1.25 mL) was then added dropwise and the resulting mixture was stirred in the absence of light overnight. On the next day, the mixture was purified by preparative HPLC (C8; gradient elution H$_2$O–0.1% TFA–MeCN). Fraction with product was lyophilized. Resulting product was obtained as a white substance (16.3 mg; 66 %; 1 step; based on *N*-hydroxysuccinimidester of 4-dibenzocyclooctynamidobutanoic acid).

NMR (D$_2$O): **^{1}H** δ 1.42 (CH$_2$—C*H*$_2$—CH$_2$, m, 2H); 1.77 (C*H*$_2$, m, 1H); 1.85 (C*H*$_2$—C—P, tm, $^{3}J_{HP}$ = 13 Hz); 1.96 (C*H*$_2$, t, 2H, $^{3}J_{HH}$ = 7 Hz); 2.16 (C*H*$_2$, m, 1H); 2.88 (C*H*$_2$—NH, t, $^{3}J_{HH}$ = 9 Hz); 3.61 (C*H*$_2$—N—CO, d, 1H, $^{2}J_{HH}$ = 14 Hz); 5.04 (C*H*$_2$—N—CO, d, 1H, $^{2}J_{HH}$ = 14 Hz); 7.29 (C*H*, d, 1H, $^{3}J_{HH}$ = 7 Hz); 7.35 (C*H*, t, 1H, $^{3}J_{HH}$ = 7 Hz); 7.39 (C*H*, t, 1H, $^{3}J_{HH}$ = 7 Hz); 7.42–7.53 (C*H*, m, 3H); 7.58 (C*H*, d, 1H, $^{3}J_{HH}$ = 7 Hz); 7.63 (C*H*, t, 1H, $^{3}J_{HH}$ = 7 Hz); **^{31}P**{^{1}H} δ 21.2 (m, 1P).

MS: (−) 516.9 [M−H_3O^+]$^-$; 534.8 [M−H^+]$^-$. (+) 536.2 [M+H^+]$^+$; 559.2 [M+Na^+]$^+$; 581.1 [M−H^++2Na^+]$^+$.

TLC (SiO_2, EtOH–conc. aq. NH_4OH 1:1): R_f = 0.

Example 52: *Synthesis of conjugate* ***46***



In a glass vial (4 mL), **40**·3H_2O (14.1 mg; 19.1 μmol; 1.0 equiv.) was dissolved in aqueous buffer AcOH–NH_3 (500 mM; 700 μL; 350 μmol; 18 equiv.). Freshly prepared solution of intermediate **F** (11.6 mg; 21.6 μmol; 1.1 equiv.) in a mixture of DMSO–MeCN–H_2O (1:1:1; 800 μL) was then added and the resulting solution was stirred at room temperature for three hours. The crude product was purified by preparative HPLC (C8; gradient elution H_2O–0.1% TFA–MeCN). Fraction with product was lyophilized. Resulting product (mixture of two regioisomers) was obtained as a white substance (14.1 mg; 56 %; 1 step; based on **40**·3H_2O).

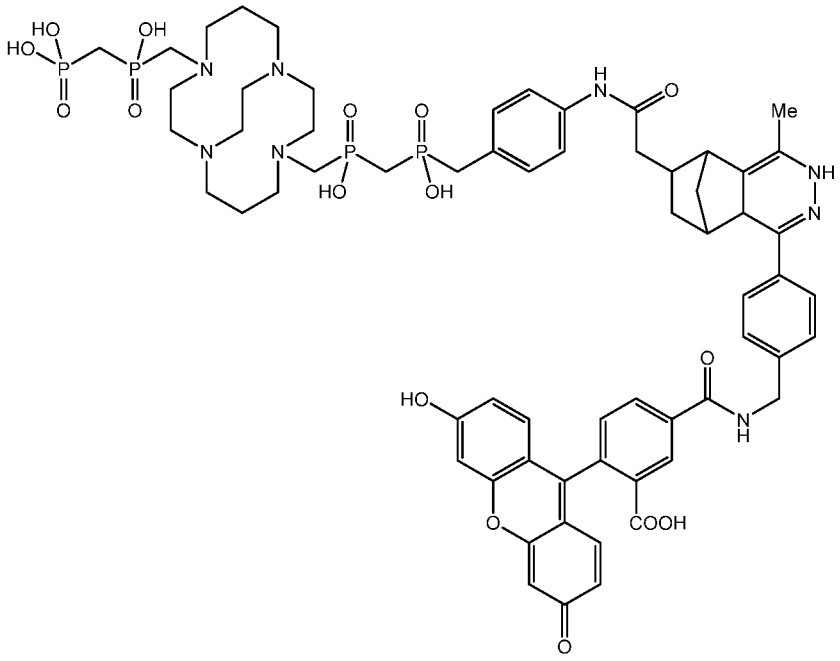
NMR (D_2O): **^{1}H** δ 1.22–1.41 (CH_2, bm, 4H); 1.83–1.99 (CH_2—C—P, CH_2, bm, 6H); 2.05 (CH_2, m, 2H); 2.14–2.45 (P—CH_2—P, CH_2, bm, 6H); 2.63–3.68 (*cycle*, P—CH_2—C, P—CH_2—N, bm, 26H); 4.52–5.07 (CH_2—N—CO, m, 1H); 5.63–5.79 (CH_2—N—CO, m, 1H); 6.94 (C*H*, d, 1H, $^3J_{HH}$ = 8 Hz); 7.02–7.22 (C*H*, m, 1H); 7.02–7.22 (C*H*, m, 1H); 7.30 (C*H*, bm, 2H); 7.34–7.61 (C*H*, bm, 7H); **^{31}P**{^{1}H} δ 14.4 (HO—*P*—OH, bm, 1P); 18.4 (*P*O_3H_2, bm, 2P); 24.4–28.9 (*P*—CH_2—N, bm, 2P); 33.6–34.7 (*P*—CH_2—C, bm, 1P).

MS: (−) 1202.5 [M−H_3O^+]$^-$; 1220.5 [M−H^+]$^-$. (+) 1222.7 [M+H^+]$^+$.

TLC (SiO_2, EtOH–conc. aq. NH_4OH 1:1): R_f = start.

EA ($C_{46}H_{69}N_9O_{18}P_6$·5.5H_2O, M_R = 1321.0): C 41.8 (41.8); H 6.1 (6.0); N 9.5 (9.5).

Example 53: *Synthesis of targeting conjugate* ***47***



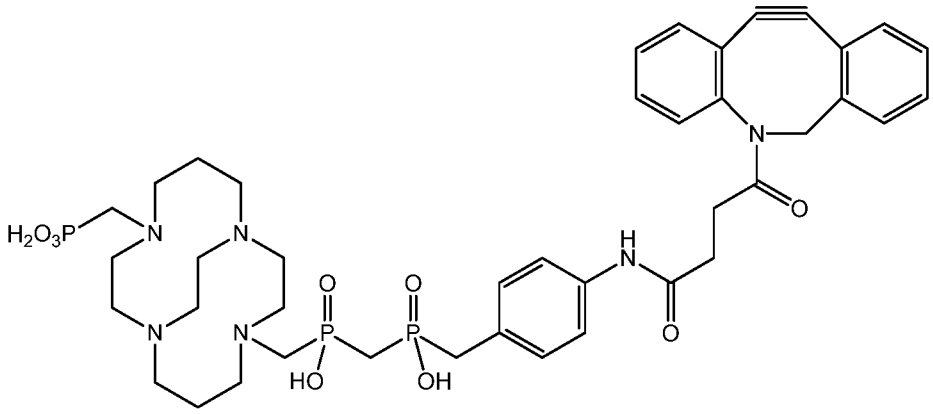
In a glass vial (4 mL), fluorescein-6-methyl-tetrazine conjugate (1.0 mg; 1.8 μmol; 1.0 equiv.) was dissolved in dry DMSO (500 μL) followed by addition of freshly prepared solution of **45**·TFA·2H_2O (2.5 mg; 2.7 μmol; 1.0 equiv.) in aqueous buffer AcOH–NH_3 (100 mM; 500 μL; 50 μmol; 28 equiv.). The resulting mixture was stirred at room temperature overnight. The crude product was purified by preparative HPLC (C8; gradient elution H_2O–0.1% TFA–MeCN). Fraction with product was lyophilized. Resulting product (mixture of two regioisomers) was obtained as a white substance (≈2 mg).

NMR (D_2O): **^{1}H** δ 1.46 (CH—CH_2—CH, m, 1H); 1.62 (CH_2, bm, 1H); 1.88–1.96 (*cycle*, CH—CH_2—CH, bm, 2H); 1.98–2.16 (P—CH_2—P, *cycle*, bm, 3H); 2.25 (P—CH_2—P, dd, 2H, $^2J_{HP}$ = 17 Hz, $^2J_{HP}$ = 15 Hz); 2.32 (CH_3, s, 3H); 2.63–4.03 (*cycle*, *CH*, N—CH_2—P, P—CH_2—C, bm, 33H); 6.66 (C*H*, m, 1H); 6.82–6.84 (C*H*, bm, 3H); 6.97 (C*H*, d, 2H, $^3J_{HH}$ = 7 Hz); 7.12–7.23 (C*H*, bm, 3H); 7.29 (C*H*, d, 2H, $^3J_{HH}$ = 9 Hz); 7.34 (C*H*, d, 1H, $^3J_{HH}$ = 7 Hz); 8.03 (d, 2H, $^3J_{HH}$ = 8 Hz); **^{31}P**{^{1}H} δ 14.8 (HO—*P*—OH, d, 1P, $^2J_{PP}$ = 8 Hz); 28.9 (*P*—CH_2—N, m, 1P); 32.1 (*P*—CH_2—N, m, 1P); 36.2 (*P*—CH_2—C, d, 1P, $^2J_{PP}$ = 10 Hz).

MS: (−) 1323.8 [M−H^+]$^-$. (+) 1369.7 [M−H^++2Na^+]$^+$.

TLC (SiO_2, *i*PrOH–conc. aq. NH_4OH–H_2O 7:3:3): R_f = 0.3.

Example 54: *Synthesis of conjugate* ***48***



In a glass vial (4 mL), **43**·3H_2O (28.9 mg; 45.5 μmol; 1.0 equiv.) was dissolved in a mixture of aqueous buffer H_3PO_4–NaOH (1.0 M, pH = 8.1; 1.00 mL) and MeCN (0.5 mL) and the resulting solution was cooled in an ice bath (5 °C). Solution of *N*-hydroxysuccinimidester of 4-dibenzocyclooctynamidobutanoic acid (36.2 mg; 90.0 μmol; 2.0 equiv.) in dry DMSO (1.7 mL) was then added dropwise and the resulting solution was stirred in the absence of light overnight. On the next day, the mixture was purified by preparative HPLC (C8; gradient elution H_2O–0,1% TFA–MeCN). Fraction with product was directly lyophilized. Product was obtained as a violet substance (24.6 mg; 63 %; 1 step; based on **43**·3H_2O).

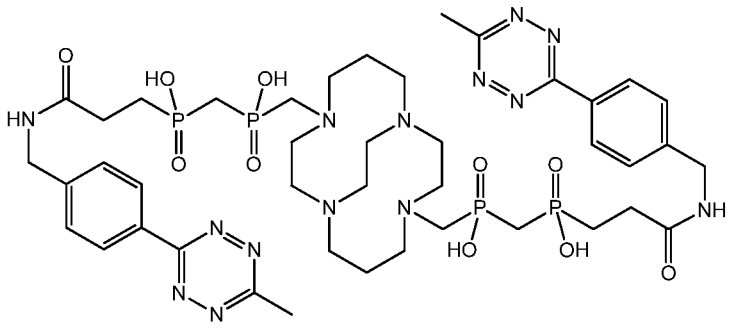
NMR (D_2O): ^{31}**P**{^{1}H} δ 12.2 (HO—*P*—OH, s, 1P); 19.4 (*P*—CH_2—*P*, d, 1P, $^2J_{PP}$ = 10 Hz); 38.2 (*P*—CH_2—*P*, d, 1P, , $^2J_{PP}$ = 10 Hz).

MS: (−) 867.6 $[M-H^+]^-$. (+) 870.2 $[M+H^+]^+$; 892.1 $[M+Na^+]^+$; 907.7 $[M+K^+]^+$.

TLC (SiO_2, EtOH–conc. aq. NH_4OH 2:1): R_f = 0.4.

EA ($C_{41}H_{55}N_6O_9P_3$·2.5H_2O, M_R = 913.9): C 53.6 (53.9); H 6.8 (6.6); N 8.9 (9.2).

Example 55: *Synthesis of conjugate* ***49***



Compound **35**·2H_2O (108 mg; 150 μmol; 1.0 equiv.) and *N*-hydroxysuccinimide (NHS; 69 mg; 600 μmol; 4.0 equiv.) were dissolved in aqueous acetate buffer HOAc/NaOAc (pH 5.5; 0.5 M; 3 mL). To this solution, EDC·HCl (186 mg; 1.20 mmol; 8 equiv.) in the same buffer (1 mL) was added. Carboxylate functions were activated for 30 min and then pH of this solution was adjusted to 9 using aqueous NaOH (0.05 M). Solution of methyltetrazinamine hydrochloride (78.4 mg; 330 μmol; 2.2 equiv.) in dry DMSO (2.0 mL) was then added and the pH was re-adjusted to 8 using aqueous NaOH (0.05 M). The mixture was stirred at room temperature for three hours. The mixture was then concentrated to 2 mL volume and subsequently purified by preparative HPLC (C8; gradient elution H_2O–0.1% TFA–MeCN). Fraction with product was directly lyophilized. Product was obtained as a violet substance (121 mg; 75 %; 1 step; based on **35**·2H_2O).

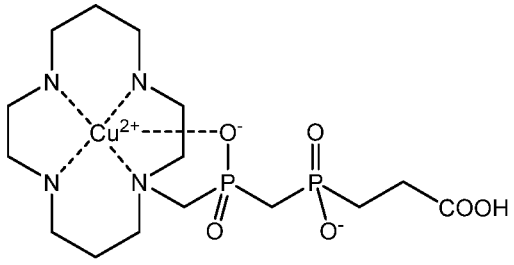
NMR (D_2O): **^{1}H** δ 1.82 (CH_2—CH_2—CH_2, m, 2H); 1.88 (CH_2—CH_2—CH_2, m, 2H); 1.99 (P—CH_2—C, m, 4H); 2.13 (P—CH_2—P, m, 4H); 2.34 (CH_3, s, 6H); 2.40 (CH_2—CO, t, 4H, $^3J_{HH}$ = 7 Hz); 2.72–3.22 (*cycle*, bm, 20H); 3.34 (N—CH_2—P, m, 4H); 4.31 (CH_2—NH—CO, s, 4H); 7.11 (C*H*, d, 2H, $^3J_{HH}$ = 8 Hz); 8.11 (C*H*, d, 2H, $^3J_{HH}$ = 8 Hz); **^{13}C**{^{1}H} δ 19.4 (*C*H_3, s); 22.1 (CH_2—*C*H_2—CH_2, s); 28.0 (P—*C*H_2—C, d, $^1J_{CP}$ = 93 Hz); 29.3 (*C*H_2—CO, s); 35.5 (P—*C*H_2—P, dd, $^1J_{CP}$ = 79 Hz, $^1J_{CP}$ = 75 Hz); 44.2 (*C*H_2—NH—CO, s); 50.1 (*cycle*, s); 54.2 (*cycle*, s); 55.8 (*cyclus*, d, $^3J_{CP}$ = 5 Hz); 56.2 (N—*C*H_2—P, d, $^1J_{CP}$ = 102 Hz); 58.2 (*cycle*, s); 59.0 (*cycle*, d, 3); 122.6 (*arom.*, s); 127.3 (*arom.*, s); 129.6 (*arom.*, s); 138.2 (*arom.*, s); 161.2 (*arom.*, s); 164.2 (*arom.*, s); 174.2 (*C*O, d, $^3J_{CP}$ = 17 Hz); **^{31}P**{^{1}H} δ 27.2 (CH_2—*P*—CH_2, bm, 2P); 36.1 (CH_2—*P*—CH_2, d, 2P, $^2J_{PP}$ = 8 Hz).

MS: (−) 1048.1 [M−H^+]$^-$. (+) 1050.3 [M+H^+]$^+$; 1072.2 [M+Na^+]$^+$; 1087.6 [M+K^+]$^+$.

TLC (SiO_2, EtOH–conc. aq. NH_4OH 2:1): R_f = 0.4.

EA ($C_{42}H_{64}N_{14}O_{10}P_4$·1.5$H_2O$, M_R = 1076.0): C 46.6 (46.9); H 6.2 (6.0); N 17.8 (18.2).

Example 56: *Synthesis of copper(II) complex of compound* ***14***



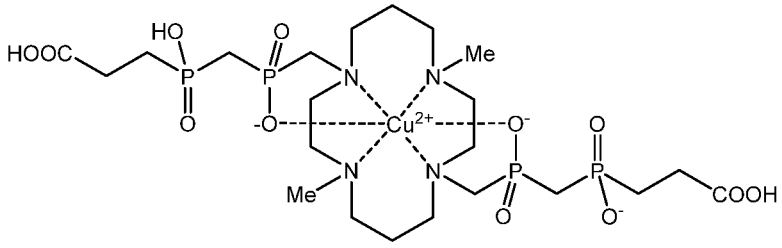
In a glass vial (4 mL), weighted amount of compound **14**·4H_2O (61.3 mg; 122 μmol; 1.0 equiv.) and $Cu(OAc)_2$·H_2O (34.2 mg; 171 μmol; 1.4 equiv.) was dissolved in aqueous pyridine (2 %; 3 mL) and the mixture was stirred for 10 min. Subsequently, the reaction mixture was evaporated to dryness and then several times co-evaporated with water. The crude complex was purified on ion exchange resin (DOWEX 50; H^+-forma; water elution). Fractions containing the product were combined and evaporated to dryness. The residue was re-dissolved in water (50 mL) and the solution was lyophilized. The final product was obtained as dark blue material (51.4 mg; 83 %; 1 step; based on **14**·4H_2O).

MS: (−) 488,0 $[M-H^+]^-$; 524,0 $[M+Cl^-]^-$. (+) 449,0 $[M+H^+]^+$; 512,0 $[M+Na^+]^+$.

TLC (SiO_2, *i*PrOH–konc. NH_4OH–H_2O 7:3:3): R_f = 0,4.

EA ($C_{15}H_{32}N_4O_6P_2Cu$·H_2O, M_R = 508,0): C 35,5 (35,7); H 6,8 (6,6); N 11,0 (11,1).

Example 57: *Synthesis of copper(II) complex of compound* ***23***



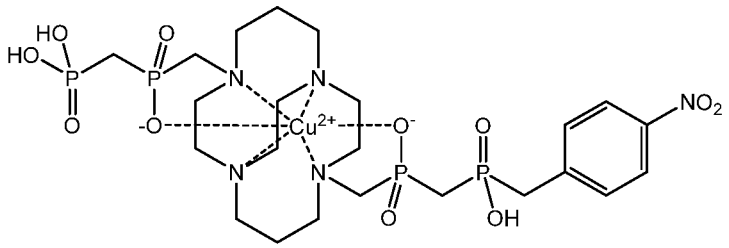
In a glass vial (4 mL), weighted amount of compound **23**·3H_2O (98.7 mg; 134 μmol; 1.0 equiv.) and $Cu(OAc)_2$·H_2O (41.2 mg; 206 μmol; 1.5 equiv.) was dissolved in aqueous pyridine (5 %; 3 mL) and the mixture was stirred for 10 min. Subsequently, the reaction mixture was evaporated to dryness and then several times co-evaporated with water. The crude complex was purified on ion exchange resin (DOWEX 50; H^+-forma; water elution). Fractions containing the product were combined and evaporated to dryness. The residue was re-dissolved in water (100 mL) and the solution was lyophilized. The final product was obtained as dark blue material (83.4 mg; 77 %; 1 step; based on **23**·3H_2O).

MS: (−) 743,2 $[M-H^+]^-$.

TLC (SiO_2, *i*PrOH–konc. NH_4OH–H_2O 7:3:3): R_f = 0,2.

EA ($C_{22}H_{45}N_4O_{12}P_4Cu$·0,5HCl·2,5$H_2O$, M_R = 808,3): C 29,5 (29,6); H 4,8 (4,9); N 7,8 (7,8).

Example 58: *Synthesis of copper(II) complex of compound* ***37***



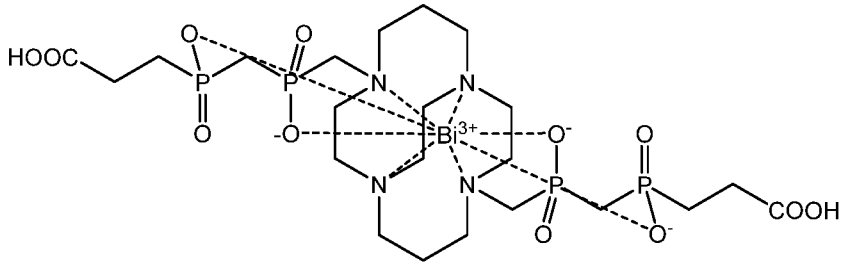
In a glass vial (4 mL), weighted amount of compound **37**·4.5H_2O (29.7 mg; 38.5 μmol; 1.0 equiv.) was dissolved in aqueous solution of $CuCl_2$ (63 mM; 793 μl; 50.0 μmol; 1.3 equiv.) and the solution pH was slowly adjusted to pH 6 with aqueous solution of NaOH. The crude complex was purified by preparative HPLC (C8; gradient elution H_2O–0.1 % TFA-MeCN). Fraction containing the product was lyophilized. The final product was obtained as light blue material (25.8 mg; 70 %; 1 step; based on **37**·4.5H_2O).

MS: (−) 749,1 $[M-H^+]^-$; 785,0 $[M+Cl^-]^-$. (+) 751,1 $[M+H^+]^+$; 774,1 $[M+Na^+]^+$; 790,2 $[M+K^+]^+$.

TLC (SiO_2, *i*PrOH–konc. NH_4OH–H_2O 7:3:3): R_f = 0,2.

EA ($C_{23}H_{41}N_5O_{11}P_4Cu$·0,5TFA·3$H_2O$, M_R = 953,5): C 30,2 (30,1); H 5,0 (5,0); N 7,3 (7,4).

Example 59: *Synthesis of bismuth(III) complex of compound* ***35***



In a glass vial (4 mL), weighted amount of compound **35**·2H_2O (34.4 mg; 47.8 μmol; 1.0 equiv.) was dissolved in aqueous solution of $Bi(NO_3)_3$ (50.5 mM; 947 μl; 47.8 μmol; 1.0 equiv.) and the solution pH was slowly adjusted to pH 5with solid urotropine. The reaction mixture was heated at 90 °C for 2 h. Then, further solid urotropine was added to increase pH to 5. The reaction mixture was heated at 90 °C for 6 h. After cooling, the reaction mixture was evaporated to dryness. The crude complex was purified on ion exchange resin (Amberlite CG50; H^+-forma; water elution). Fractions containing the product were combined and evaporated to dryness. The residue was re-dissolved in

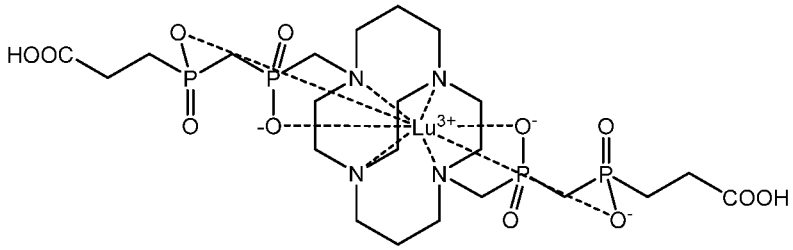
water (50 mL) and the solution was lyophilized. The final product was obtained as white material (34.3 mg; 75 %; 1 step; based on **35**·2H_2O).

MS: (−) 887,2 $[M-H^+]^-$. (+) 889,2 $[M+H^+]^+$.

TLC (SiO_2, *i*PrOH–konc. NH_4OH–H_2O 7:3:3): R_f = 0,4.

EA ($C_{22}H_{43}N_4O_{12}P_4Bi·2H_2O$, M_R = 955,5): C 28,6 (28,5); H 5,1 (4,9); N 6,1 (6,3).

Example 60: *Synthesis of lutetium(III) complex of compound* ***35***



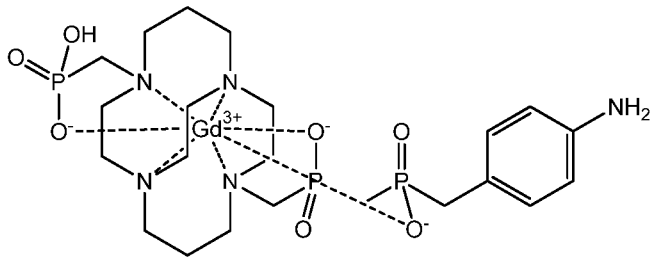
In a glass vial (4 mL), weighted amount of compound **35**·2H_2O (44.1 mg; 61.4 μmol; 1.0 equiv.) was dissolved in aqueous solution of $LuCl_3$ (50.1 mM; 1.23 ml; 61.6 μmol; 1.0 equiv.) and the solution pH was slowly adjusted to pH 7 with aqueous NaOH. The reaction mixture was heated at 80 °C overnight. Next day, the reaction mixture was evaporated to dryness and the crude complex was purified on ion exchange resin (Amberlite CG50; H^+-forma; water elution). Fractions containing the product were combined and evaporated to dryness. The residue was re-dissolved in water (50 mL) and the solution was lyophilized. The final product was obtained as white material (37.1 mg; 64 %; 1 step; based on **35**·2H_2O).

MS: (−) 853,1 $[M-H^+]^-$. (+) 855,1 $[M+H^+]^+$; 893,1 $[M+K^+]^+$.

TLC (SiO_2, EtOH–konc. NH_4OH 1:1): R_f = 0,6.

EA ($C_{22}H_{43}N_4O_{12}P_4Lu·5H_2O$, M_R = 944,5): C 28,0 (28,0); H 5,7 (5,9); N 5,9 (5,9).

Example 61: *Synthesis of gadolinium(III) complex of compound* ***43***



In a glass vial (4 mL), weighted amount of compound **43**·3H_2O (62.5 mg; 66.2 μmol; 1.0 equiv.) was dissolved in aqueous solution of $GdCl_3$ (49.8 mM; 1.33 ml; 66.2

μmol; 1.0 equiv.) and the solution pH was slowly adjusted to pH 6. The reaction mixture was heated at 80 °C for 2 h. Then, pH was increased to 5 with aqueous NaOH and the reaction mixture was heated at 80 °C overnight. Next day, the reaction mixture was evaporated to dryness and the crude complex was purified on ion exchange resin (Amberlite CG50; H^+-forma; water elution followed with 10 % AcOH in mixture of water:EtOH 1:1). Fractions containing the product were combined and evaporated to dryness. The residue was re-dissolved in water (50 mL), evaporated to dryness and dissolved in water again (50 mL) and the solution was lyophilized. The final product was obtained as white material (37.1 mg; 75 %; 1 step; based on **43**·$3H_2O$).

MS: (−) 853,1 $[M-H^+]^-$. (+) 855,1 $[M+H^+]^+$; 893,1 $[M+K^+]^+$.

Example 62: Comparative experiment: *Labelling of the compounds with ^{64}Cu*

Aqueous solution of a compound to be labelled (1.0 mM; 1.0 μL) was added to aqueous buffer solution MES-NaOH (1.0 M; pH 6.2; 10.0 μL) in Eppendorf plastic microvial (1.5 mL). The solution was incubated with mild agitation (750 oscillations/min) at 25 °C for 10 min. To the mixture, freshly prepared $[^{64}Cu]CuCl_2$ solution in 10 mM aqueous HCl (6 μL; 9–10 MBq) was added. Then, the reaction mixture was incubated with mild agitation (750 oscillations/min) at 25 °C for 10 min. After 10 min, the reaction mixture was analysed by TLC (SiO_2 60 W F_{254} S; aqueous EDTA-NaOH buffer, pH 5; R_f(free copper) = 0.8–0.9; R_f(complex) = 0). Examples of radiochemical yields (determined by RitaStar; Raytest) of selected compounds involving also examples of currently used ligands (in italics) are given below (for each ligand, labelling was carried out with three different batches-eluates of $[^{64}Cu]CuCl_2$):

Compound	Radiochemical yield
1	71±10%
8	76±14%
14	83±8%
19	83±9%
32	83±3%
34	62±12%
41	66±8%
NOTA	*18±11%*

DOTA	*9±7%*
cb-TE2A	*2±1%*

Radiochemical yields for the compounds which are subject of the patent application were, under identical conditions, several times better than those of commercial ligands as NOTA, DOTA a *cb*-TE2A.

Example 63: *Labelling of compound **34** with ^{177}Lu*

Aqueous solution of the non-carrier-added [^{177}Lu]$LuCl_3$ in 0.01 M HCl (50 μL, ca. 12 MBq activity) was added to aqueous solution of NH_4OAc (0.2 mL of the buffer; pH 5.5; 1 M) in a 1-mL vial. To the solution, a solution of the compound **34** in ultrapure water was added (40 μL, c = 50 μM) and the solution was agitated at 90 °C for 20 min. ITLC analysis (1 M aqueous NH_4OAc : MeOH; 1:1 v/v) confirms presence of the radiochemically pure labelled complex (complex with R_f ~0.9; free ^{177}Lu has R_f = 0).

Example 64: *Labelling of compound **37** with ^{213}Bi*

Aqueous solution of NaOAc (pH 5.5; 1 M; 1.6 mL) was added to the non-carrier-added $^{213}Bi^{3+}$ present as a solution in 0.15 M aqueous KI (1.4 mL) with a nominal activity ca. 150 MBq (i.e. ca. 107 MBq/mL). To the solution of compound **37** in ultrapure water (10 μL, c = 100 μM), a solution containing [^{213}Bi]Bi^{3+} (90 μL, ca. 10 MBq) was added and the solution was incubated at 70 °C for 10 min. Paper liquid chromatography (0.1 M aqueous Na-citrate) showed a quantitative complex formation (R_f(complex) <0.5, ^{213}Bi-citrate moves with the solvent front).

Example 65: *Synthesis of targeting conjugate of the compound **39** and the Rituximab antibody*

Water used to prepare reaction solutions and used for purifications in the Example is deionized water which was purified from possible metal impurities by ion exchange on Chelex 100 chelating resin. Throughout the procedure, sterile glassware and plastics was used, used commercial chemicals have the highest available purity in a view of metal ion content.

Aqueous solution (4 mL) of Rituximab antibody (0.14 μmol) having concentratio 5.0 mg/mL was concentrated by ultrafiltration in MWCO-30 kDa Vivaspin 6 vial to 1 mL (final concentration 20 mg/mL). This concentrated antibody solution was incubated with

a solution of compound **39**·3.5H_2O (1.1 mg; 1.4 μmol, antibody:ligand 1:10 molar ratio) in anhydrous DMSO (200 μl; dissolved under sonification, sterilized by filtration through syringe microfilter; Millipore, 0.22 μm). Immediately after the reaction mixture preparation, the solution pH was adjusted to 8.2–8.6 with 0.1 M aqueous NaOH solution. The reaction mixture was agitated (Vortex, 450 rev./min.) at room temperature for 2 h. One hour after start of the reaction, pH was re-adjusted to 8.2–8.6 (0.1 M aqueous NaOH). The conjugation was terminated by TRIS-HCl buffer solution (1.0 M; pH 8.8; 50 μL) addition. The conjugate solution was purified from unreacted ligand and other low-molecular-weight impurities by triplicate ultrafiltration with utilization of Vivaspin 6. The ultrafiltration was carried out by the following procedure. The mixture was transferred into washed sterilized Vivaspin 6 vial and the solution volume was adjusted to 6 mL with 0,1 M PBS buffer (pH 8.5). Then, upper part of the Vivaspin vial was incubated in Vortex (1000 oscillations/min) for 5 min. Then, the solution was centrifugated at 4000 rev./min for 45 min to get 0.3 mL solution volume in the upper part of the Vivaspin vial. The antibody solution in the upper part of the vial was adjusted to 6 mL with 0,05 M aqueous NH_4OAc (pH 7.0), and the step vortexing-centrifugation was repeated (carried out 2-times). After the third centrifugation, the solution containing the antibody was added with water to get the final volume 3 mL. The conjugate purity was checked by spectrophotometry at 280 nm and also by HPLC (UV detection, 280 nm); degradation test and test of the antibody significant losses. The purified conjugate must be stored in the fridge at 4–8 °C temperature. An average number of the chelates per the antibody molecule was determined by MS-MALDI/TOF to be 3.

Example 66: *Labelling of targeting conjugate of the compound **39** and the Rituximab antibody with 64-Cu*

The conjugate solution from the Example 65 (0.5 mL) was transferred into Eppendorf plastic microvial (volume 1.5 mL) and, if necessary, its final volume (taking into account also the added radionuclide solution) was adjusted to 1 mL with 0.5 M NH_4OAc (pH 6.0). The solution was incubated with mild agitation (450 oscillations/min) at 25 °C for 15 min. To the mixture, non-carrier-added radiocopper [^{64}Cu]$CuCl_2$ solution in 0.01 M aqueous HCl (0.12 mL; 200 MBq [^{64}Cu]$CuCl_2$) was added. Subsequently, solution pH was checked and was found to be 6.0. Then, the reaction mixture was incubated with mild agitation (450 oscillations/min) at 40 °C for 20 min. Once incubation

was finished, the labelled conjugate was sterilized by filtration through syringe microfilter (Millipore; 0,22 μm). ITLC analysis (1 M aqueous NH_4OAc and MeOH; 1:1 v/v) carried out after addition of aqueous DTPA (to bind free 64-Cu) to the sterile sample showed radiochemically pure labelled conjugate (R_f = 0) and no free 64-Cu (Cu-DTPA, R_f ~0,9).

Example 67: *Synthesis of conjugate of the compound **39** and the PAMAM dendrimer of the second generation*

Commercial form of the G2-PAMAM dendrimer (16 free amino groups; 20 % solution in MeOH; 0.15 mL; 10 μmol) was dissolved in H_2O (5 mL) and the compound **39** (127 mg; 160 μmol; equivalent amount per amino groups on the dendrimer) was dissolved in this solution. Solution pH was carefully adjusted to 9 with aqueous KOH solution and the reaction mixture was stirred at 40 °C for 12 h. Then, compound **39** (63 mg; 0,5 molar equivalent per dendrimer amino groups) was added again, pH was re-adjusted to 9 aqueous KOH solution and the solution was stirred at 40 °C for 12 h. Then, the solution was cooled down, solution pH was decreased to pH = 7 and the solution was filtrated through syringe microfilter (Millipore; 0.22 μm) into ultrafiltration cell. Ultrafiltration (under 3 atm pressure, 3-kDa membrane cut-off) was carried out three times from volume 50 mL to the retenate volume 10 mL, and it was followed by continuous ultrafiltration (4 atm) until 800 ml of the filtrate was obtained. The retenate was lyophilized to give white solids (167 mg; with the active compound content 72 %, the yield is 83 % based on the starting dendrimer). A number of ligand moieties in the dendrimer conjugate (^{1}H NMR spectrum) was estimated to be 15.5.

NMR (D_2O): **^{1}H** δ 1,88–3,72 (CH_2, bm, 39,44H); 7,11–7,33 (CH, bm, 4,00H); **^{31}P**{^{1}H} δ 19,0 (HO—*P*—OH, bm, 1P); 23,8 (*P*—CH_2—*P*, bm, 1P); 28,2 (*P*—CH_2—*P*, bm); 35,8 (*P*—CH_2—*P*, bm, 1P).

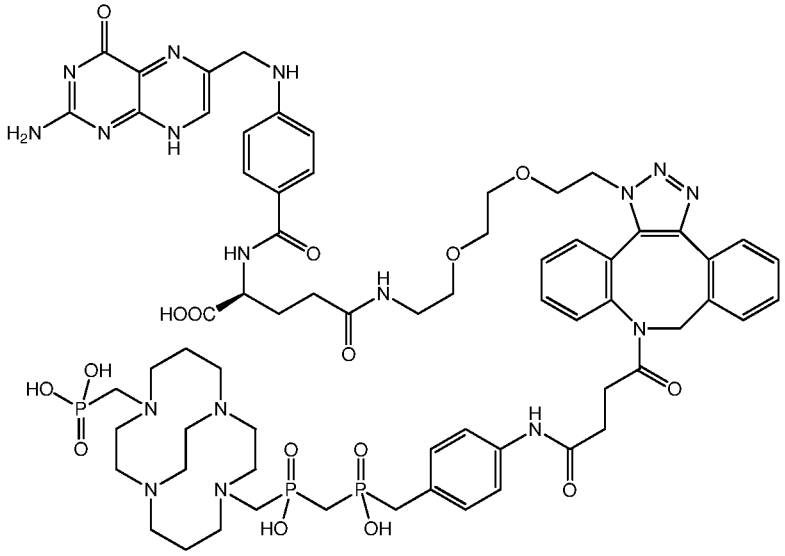
EA (M_w of the pure dendrimer conjugate ~14482): 31.4% C, 8.0% H, 9.6%N, 2.5% S; i.e. dendrimer conjugate content was 72 %.

Example 68: *Labelling of targeting conjugate of the compound **39** and the PAMAM dendrimer of the second generation with 64-Cu*

The conjugate from Example 67 (5 mg, ca. 0.25 μmol, ca. 3.9 μmol of the macrocycle) was dissolved in ultrapure water (50 μL) in an Eppendorf plastic microvial

(0.5 mL) and aqueous buffer HOAc/NaOAc (0.5 M, pH 5.8; 0.2 mL) was added. To the mixture, non-carrier-added [^{64}Cu]$CuCl_2$ in 0.01 M aqueous HCl (120 μL, 180–200 MBq [^{64}Cu]$CuCl_2$) was added. Subsequently, solution pH was checked and was found to be 5.8. Then, the reaction mixture was incubated with mild agitation (450 oscillations/min) at 50 °C for 20 min. It led to a solution containing the labelled dendrimer. The product was analysed by thin-layer chromatography (Instant Thin-Layer Chromatography ITLC) on plates with impregnated glass fibres as stationary phase and with 10 mM EDTA in 0.1 M aqueous NH_4OAc (pH 5.5) as a mobile phase (R_f = 0–0.1) and radioactivity was detected only in the spot of the dendrimer.

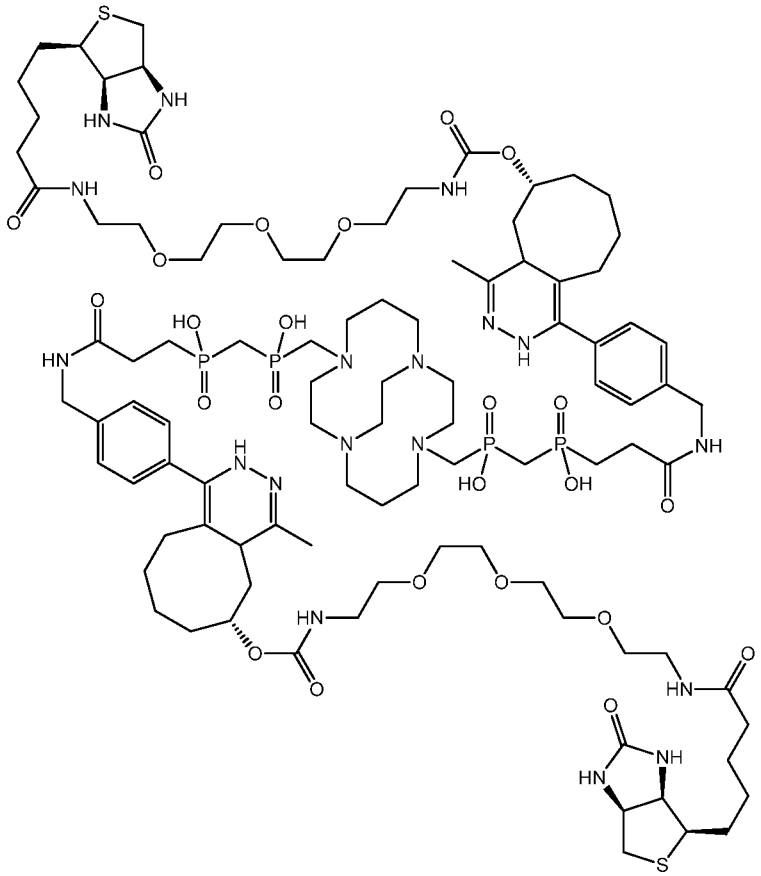
Example 69: *Synthesis of targeting conjugate with folic acid, based on conjugate* ***48***



In a glass vial (4 mL), the weighted amount of conjugate **48**·2.5 H_2O (11 mg; 12 μmol; 1.0 equiv.) was dissolved in aqueous NH_4OAc buffer (500 mM; pH 5.0; 0.5 mL). To the solution, freshly prepared solution of δ-(1-azido-3,6-dioxaoktan-8-amide) of folic acid (8.6 mg; 14.4 μmol; 1.2 equiv.) in water (0.3 mL) was added. The mixture was stirred at room temperature for 4 h. The crude product was purified by preparative HPLC (C8; gradient elution H_2O–0.1% TFA–MeCN). Fraction with product was lyophilized. The final product was obtained as a mixture of regioisomers as a white substance (11.4 mg).

MS: (+) 1467.6 $[M+H^+]^+$, 1489.2 $[M+Na^+]^+$.

Example 70: *Synthesis of targeting conjugate with biotin, based on conjugate* ***49***

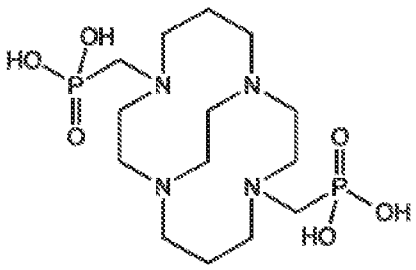


In a glass vial (4 mL), the weighted amount of conjugate **49**·1.5 H_2O (11.8 mg; 11 μmol; 1.0 equiv.) was dissolved in water, NH_4OAc (500 mM; pH 5.0; 0.5 mL). To the solution, freshly prepared solution of commercial biotin derivative TCO-PEG3-biotin (7.5 mg; 13.2 μmol; 1.2 equiv.) in water (0.4 mL) was added. The mixture was stirred at room temperature for 30 min. The crude product was purified by preparative HPLC (C8; gradient elution H_2O–0.1% TFA–MeCN). Fraction with product was lyophilized. The final product was obtained as a mixture of regioisomers as a white substance (15.2 mg).

MS: (+) 1590,5 $[M+H^+]^+$, 1612,8 $[M+Na^+]^+$.

Example 71: Comparative experiment: *Labelling of compounds according to the present invention and the compound cb-TE2P, representing the state-of-the-art, with* ^{64}Cu

Structural formula of *cb*-TE2P



Aqueous solution of a compound to be labelled (1.0 mM; 1.0 μL) was added to aqueous buffer solution MES-NaOH (1.0 M; pH 5.5; 10.0 μL) in Eppendorf plastic microvial (1.5 mL). The solution was incubated with mild agitation (750 oscillations/min) at 25 °C for 10 min. To the mixture, freshly prepared [^{64}Cu]$CuCl_2$ solution in 10 mM aqueous HCl (6 μL; 9–10 MBq) was added. Then, the reaction mixture was incubated with mild agitation (750 oscillations/min) at 25 °C for 60 min. After 60 min, the reaction mixture was analysed by TLC (SiO_2 60 W F_{254} S; aqueous EDTA-NaOH buffer, pH 5; R_f(free copper) = 0.8–0.9; R_f(complex) = 0). Examples of radiochemical yields (determined by RitaStar; Raytest) of the selected compounds involving also examples of currently used ligands (in italics) are given below (for each ligand, labelling was carried out with at least three different batches-eluates of [^{64}Cu]$CuCl_2$). The same procedure was used at pH 6.2, but the reaction mixture was incubated only 10 min. Results are summarized in Table 1.

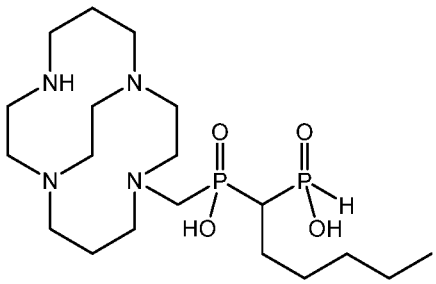
Table 1: Radiochemical yield (%) in labelling of compounds of the present invention and their analogues at two pH values.

LIGAND	pH 6.2	pH 5.5
8	76±14	79
32	83±3	82
37	90±13	99
NOTA	18±11	26
DOTA	9±7	35
cb-TE2A	2±1	1
cb-TE2P	46±7	5

Radiochemical yield for compounds which are subject of the present invention at pH 6.2 significantly surpasses those of the state-of-the-art ligands (NOTA, DOTA, *cb*-TE2A, *cb*-TE2P). In the labelling at pH 5.5 (it was chosen as, at this pH, there is a smaller

complexation competition with Zn^{2+} a Ni^{2+} which are product of the ^{64}Cu radioactive decay), the difference between claimed compounds and the state-of-the-art ligands is huge.

Example 72: *Synthesis of compound* ***50***



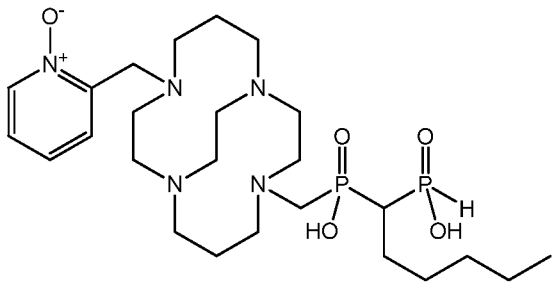
To a glass vial (20 mL), 1,4,8,11-tetraazabicyklo[6.6.2]hexadekan (881 mg; 3.89 mmol; 2.2 equiv.) was weighted. Subsequently, hexan-1,1-diyl-bis(phosphinic acid) (synthesized according to S. Gouault-Bironneau et al. *Org. Lett.* 2005, **7**, 5909–5912; 1.14 g; 5.33 mmol; 3.0 equiv.), paraformaldehyd (53.0 mg; 1.77 mmol; 1.0 ekviv.) and aqueous HCl (5 M; 20 mL) were added. The suspension was stirred at 80 °C overnight. Next day, the reaction mixture was evaporated to dryness and the residue was several times co-evaporated with water. The crude product was purified by ion exchange resin chromatography (Amberlite IRA 402; OH^--form; $H_2O \rightarrow$ 10 % aqueous AcOH). Acetic acid fraction with product was evaporated to dryness and then several times co-evaporated with water. The residue was dissolved in water (100 mL) and the solution was lyophilized. The final product was obtained as a white hydroscopic material (412 mg; 52 %; 1 step; based on paraformaldehyde).

NMR (D_2O): ^{1}**H** δ 0.85 (CH_3, s, 3H) 1.11–2.22 (C*H*$_2$—C*H*$_2$—C*H*$_2$—C*H*$_2$, P—C*H*—P, *cycle*, bm, 11H); 2.31 (*cycle*, m, 1H); 2.35 (*cycle*, m, 1H); 2.42–3.89 (*cycle*, N—C*H*$_2$—P bm, 22H); 7.09 (P*H*, m, 1H); ^{13}**C**{^{1}H} δ 15.0 (C*H*$_3$, s); 16.2 (C*H*$_2$, m); 18.9 (*cycle*, s); 20.1 (*cycle*, s); 22.0 (C*H*$_2$, s); 28.3 (C*H*$_2$, s); 30.3 (C*H*$_2$, s); 41.2 (P—*C*H—P, m); 41.9 (*cycle*, s); 44.2 (*cycle*, s); 46.3 (*cycle*, s); 48.8 (*cycle*, s); 50.3 (*C*H$_2$—N—CH$_2$—P, d, $^{3}J_{CP}$ = 8 Hz); 54.3 (*cycle*, s); 55.2 (N—*C*H$_2$—P, d, $^{1}J_{CP}$ = 91 Hz); 56.7 (*cycle*, s); 56.9 (*cycle*, s); 57.3 (*cycle*, s); 58.1 (*cycle*, s); ^{31}**P** δ 23.2 (*P*H, dm, 1P, $^{1}J_{PH}$ = 528 Hz); 29.8 (*P*—CH$_2$—N, m, 1P).

MS: (−) 451.4 [M−H$^+$]$^-$; 473.4 [M−2H$^+$+Na$^+$]$^-$. (+) 453.5 [M+H$^+$]$^+$; 475.4 [M+Na$^+$]$^+$; 497.5 [M−H$^+$+2Na$^+$]$^+$.

EA ($C_{19}H_{42}N_4O_4P_2 \cdot 3H_2O$, M_R = 506.6): C 45.1 (45.4); H 9.6 (9.2); N 11.1 (10.9).

Example 73: *Synthesis of compound* ***51***



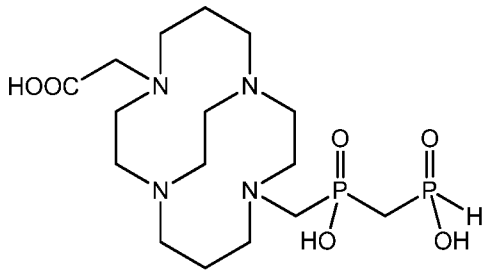
Into a glass vial (20 mL), compound **50**·3H_2O (224 mg; 501 μmol; 1.0 equiv.) a (chloromethyl)pyridine-*N*-oxide (205 mg; 1.25 mmol; 2.5 equiv.) were weighted and, subsequently, H_2O (10 mL) and LiOH·H_2O (630 mg; 15.0 mmol; 30 equiv.) were added. Subsequently, the reaction mixture was directly purified by ion exchange resin chromatography (DOWEX 50; H^+-form; H_2O → 10 % aqueous pyridine). Pyridine fraction with product was evaporated to dryness and then several times co-evaporated with water. The crude product was further purified by preparative HPLC (C8; H_2O–0,1% TFA–MeCN). Fraction with the product was lyophilized. The final product was obtained as an off-yellow material (133 mg; 36 %; 1 step; based on **50** 3H_2O).

NMR (D_2O): **^{1}H** δ 0.87 (CH_3, s, 3H) 1.03–2.28 (CH_2—CH_2—CH_2—CH_2, P—C*H*—P, *cycle*, bm, 13H); 2.29–3.75 (*cycle*, N—CH_2—P bm, 22H); 4.25 (CH_2, bs, 2H); 7.09 (P*H*, dm, 1H, $^1J_{HP}$ = 533 Hz); 7.26–7.43 (*arom.*, m, 2H); 7.68 (*arom.*, d, 1H, $^3J_{HH}$ = 7 Hz); 8.34 (*arom.*, d, 1H, $^3J_{HH}$ = 5 Hz); **^{13}C**{^{1}H} δ 13.9 (CH_3, s); 16.2 (CH_2, m); 18.9 (*cycle*, m); 20.0 (CH_2, m); 21.8 (*cycle*, s); 28.5 (CH_2, s); 30.4 (CH_2, s); 41.8 (P—*C*H—P, bm); 42.2 (*cycle*, s); 45.3 (*cycle*, s); 46.4 (*cycle*, s); 47.9 (*cycle*, s); 50.2 (*C*H_2—N—CH_2—P, d, $^3J_{CP}$ = 8 Hz); 54.3 (*cycle*, s); 55,0 (N—*C*H_2—P, bm); 56.1 (*cycle*, s); 56.8 (*cycle*, s); 59.2 (*cycle*, s); 59.9 (*cycle*, s); 62.2 (*C*H_2, s); 125.4 (*arom.*, s); 126.8 (*arom.*, s); 143.1 (*arom.*, s); 145.0 (*arom.*, s); 156.0 (*arom.*, s); **^{31}P** δ 25,8 (*P*H, dm, 1P, $^1J_{PH}$ = 533 Hz); 35,2 (*P*—CH_2—N, m, 1P).

MS: (−) 558.1 [M−H^+]$^-$; 580.0 [M−2H^++Na^+]$^-$. (+) 582.2 [M+Na^+]$^+$; 598.1 [M+K^+]$^+$; 604.2 [M−H^++2Na^+]$^+$.

EA ($C_{25}H_{47}N_5O_5P_2$·TFA·2H_2O, M_R = 733.7): C 47.5 (47.4); H 7.1 (7.3); N 9.9 (9.5).

Example 74: *Synthesis of compound* ***52***



Into a glass vial (20 mL), compound **28**·2.5HCl·H_2O (230 mg; 468 μmol; 1.0 equiv.) and chloroacetic acid (134 mg; 1.42 mmol; 3.0 equiv.) were weighted, H_2O (10 mL) and solid LiOH·H_2O (398 mg; 9.48 mmol; 20 equiv.) were consecutively added and the mixture was heated at 60 °C for 2 days. Subsequently, the reaction mixture was directly purified by ion exchange resin chromatography (DOWEX 50; H^+-form; H_2O → 10 % aqueous pyridine). Pyridine fraction with product was evaporated to dryness and then several times co-evaporated with water. The residue was dissolved in water (50 mL) and the solution was lyophilized. The final product was obtained as a white material (174 mg; 81 %; 1 step; based on **28**·2.5HCl·H_2O).

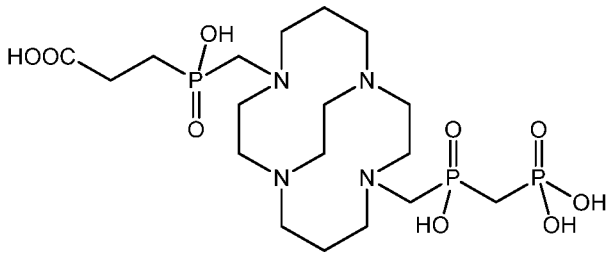
NMR (D_2O): **^{1}H** δ 1.72 (CH_2—CH_2—CH_2, m, 1H); 1.80 (CH_2—CH_2—CH_2, m, 1H); 2.08 (P—CH_2—P, t, 2H, $^2J_{PH}$ = 16 Hz); 2.30 (CH_2—CH_2—CH_2, m, 1H); 2.30 (CH_2—CH_2—CH_2, m, 1H); 2.56 (*cycle*, m, 4H); 2.84 (*cycle*, m, 3H); 3.09 (*cycle*, m, 2H); 3.15 (*cycle*, m, 2H); 3.19 (N—CH_2—P, *cycle*, 2H); 3.27 (*cycle*, m, 3H); 3.36 (*cycle*, m, 2H); 3.63 (*cycle*, m, 1H); 3.75 (N—CH_2—P, m, 1H); 3.78 (*cycle*, m, 2H); 3.89 (CH_2—COOH, s, 2H); 7.14 (P*H*, d, 1H, $^1J_{HP}$ = 535 Hz); **^{13}C**{^{1}H} δ 17.2 (CH_2—*C*H_2—CH_2, s); 19.8 (CH_2—*C*H_2—CH_2, s); 34.2 (P—*C*H_2—P, dd, $^1J_{CP}$ = 85 Hz; $^1J_{CP}$ = 77 Hz); 42.0 (*cycle*, s); 48.1 (*cycle*, s); 49.4 (*cycle*, s); 49.5 (*cycle*, s); 52.1 (*C*H_2—N—CH_2—P, d, $^3J_{CP}$ = 6 Hz); 54.0 (N—*C*H_2—P, d, $^1J_{CP}$ = 93 Hz); 54.4 (*cycle*, s); 55.8 (*cycle*, s); 56.8 (*C*H_2—COOH); 57.8 (*cycle*, s); 59.2 (*cycle*, s); 60.1 (*cycle*, s); 172.4 (*C*O, s); **^{31}P** δ 19.9 (*P*H, dt, 1P, $^1J_{PH}$ = 535 Hz, $^2J_{PH}$ = 16 Hz); 27.8 (*P*—CH_2—N, m, 1P).

MS: (−) 439.0 [M−H^+]$^-$. (+) 441.1 [M+H^+]$^+$; 463.2 [M+Na^+]$^+$; 479.1 [M+K^+]$^+$.

TLC (SiO_2, *i*PrOH–conc. aq. NH_4OH–H_2O 7:3:3): R_f = 0.2.

EA ($C_{16}H_{34}N_4O_6P_2$·H_2O, M_R = 458.4): C 41.9 (41.8); H 7.9 (7.6); N 12.2 (12.2).

Example 75: *Synthesis of compound* ***53***



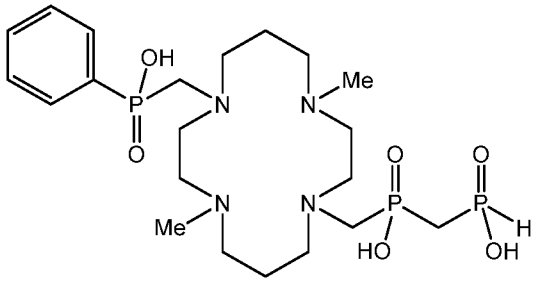
Into a glass vial (4 mL), compound **29**·1.5HCl·0.5H_2O (98.2 mg; 213 μmol; 1.0 equiv.) was weighted, and 2-carboxyethylphosphinic acid (89 mg; 644 μmol; 3.0 equiv.), paraformaldehyde (19.3 mg; 643 μmol; 3.0 equiv.) and aqueous HCl (6 M; 2 mL) were consecutively added. The suspension was stirred at 80 °C for 2 days. Next day, the reaction mixture was evaporated to dryness and the residue was several times co-evaporated with water. The crude product was purified by ion exchange resin chromatography (DOWEX 50; H^+-form; H_2O). The fraction containing a pure product were unified and lyophilized. The final product was obtained as a white material (61.9 mg; 48 %; 1 step; based on **29**·1.5HCl·0.5H_2O).

$^{31}P\{^1H\}$ δ 19.8 (HO—*P*—OH, d, 1P, $^2J_{PP}$ = 9 Hz); 27.3 (CH_2—*P*—CH_2, bm, 1P); 34.1 (CH_2—*P*—CH_2, bm, 1P).

MS: (−) 529.0 $[M-(H_3O)^+]^-$; 547.1 $[M-H^+]^-$. (+) 549.1 $[M+H^+]^+$; 571.2 $[M+Na^+]^+$; 587.2 $[M+K^+]^+$.

EA ($C_{18}H_{39}N_4O_9P_3$·3H_2O, M_R = 602.5): C 35.9 (36.3); H 7.5 (7.2); N 9.3 (9.3).

Example 76: *Synthesis of compound* ***54***



Into a glass vial (4 mL), compound **3**·3.5H_2O (112 mg; 250 μmol; 1.0 equiv.) was weighted, and phenylphosphinic acid (357mg; 2.51 mmol; 10.0 equiv.), paraformaldehyde (15.1 mg; 503 μmol; 2.0 equiv.) and aqueous HCl (12 M; 2 mL) were consecutively added. The suspension was stirred at 60 °C for 3 days. Subsequently, the reaction mixture was evaporated to dryness and the residue was

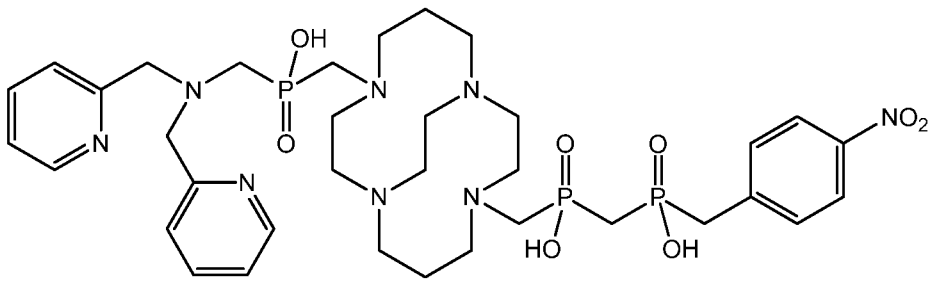
several times co-evaporated with water. The crude product was purified by preparative HPLC (C8; H_2O–0.1 % TFA–MeCN). The fraction containing product was lyophilized. The final product was obtained as a white material (104 mg; 59 %; 1 step; based on **3**·3.5H_2O).

NMR (D_2O): **^{1}H** δ 1.73 (CH_2—C*H*$_2$—CH_2, p, 2H, $^3J_{HH}$ = 7 Hz); 1.79 (CH_2—C*H*$_2$—CH_2, p, 2H, $^3J_{HH}$ = 7 Hz); 2.03 (P—C*H*$_2$—P, dd, 2H, $^2J_{HP}$ = 17 Hz, $^2J_{HP}$ = 15 Hz); 2.28 (C*H*$_3$, s, 3H); 2.33 (C*H*$_3$, s, 3H); 2.44 (*cycle*, t, 2H, $^3J_{HH}$ = 7 Hz); 2.48 (*cycle*, m, 4H); 2.71 (*cycle*, t, 2H, $^3J_{HH}$ = 6 Hz); 2.66–3.16 (*cycle*, N—C*H*$_2$—P, m, 12H); 7.09 (P*H*, dm, $^1J_{HP}$ = 534 Hz); 7.48 (*arom.*, m, 2H); 7.55 (*arom.*, m, 1H); 7.73 (*arom.*, m, 2H); **^{13}C**{^{1}H} δ 23.1 (CH_2—*C*H$_2$—CH_2, s); 23.4 (CH_2—*C*H$_2$—CH_2, s); 35.9 (P—*C*H$_2$—P, dd, $^1J_{CP}$ = 77 Hz, $^1J_{CP}$ = 75 Hz); 43.0 (*cycle*, s); 43.3 (*C*H$_3$, s); 43.6 (*C*H$_3$, s); 44.5 (*cycle*, s); 51.0 (*cycle*, d, $^3J_{CP}$ = 8 Hz); 52.2 (*cycle*, s); 54.1 (*cycle*, s); 54.3 (*cycle*, s); 54.7 (*cycle*, d, $^3J_{CP}$ = 6 Hz); 55.3 (*cycle*, s); 55.5 (N—*C*H$_2$—P, d, $^1J_{CP}$ = 109 Hz); 56.9 (N—*C*H$_2$—P, d, $^1J_{CP}$ = 101 Hz); 128.8 (*arom.*, d, $^3J_{CP}$ = 14 Hz); 131.0 (*arom.*, d, $^2J_{CP}$ = 12 Hz); 131.7 (*arom.*, d, $^1J_{CP}$ = 135 Hz); 132.8 (*arom.*, d, $^4J_{CP}$ = 3 Hz); **^{31}P** δ 23.6 (*P*H, dtm, 1P, $^1J_{PH}$ = 534 Hz, $^2J_{PH}$ = 18 Hz); 26.7 (N—CH—*P*, m, 1P) 34.2 (N—CH—*P*, m, 1P).

MS: (−) 537.2 [M−H$^+$]$^-$. (+) 539.4 [M+H$^+$]$^+$; 561.3 [M+Na$^+$]$^+$; 577.2 [M+K$^+$]$^+$.

EA ($C_{21}H_{41}N_4O_6P_3$·TFA·3H_2O, M_R = 706.6): C 39.1 (39.1); H 6.9 (6.6); N 7.9 (8.3).

Example 77: *Synthesis of compound* ***55***



Into a glass vial (20 mL), compound **35**·5.5H_2O (185 mg; 300 μmol; 1.0 equiv.) was weighted, and [di(2-picolyl)amino]methylphosphinic acid (synthesized according to J. Yu et al. *J. Am. Chem. Soc.* 2015, **137**, 14173–14179; 200 mg; 721 μmol; 2.4 equiv.), paraformaldehyde (36.4 mg; 1.21 mmol; 4.0 equiv.) and aqueous HCl (6 M; 4 mL) were consecutively added. The suspension was stirred at 80 °C for 2 days. Subsequently, the reaction mixture was evaporated to dryness and the residue was

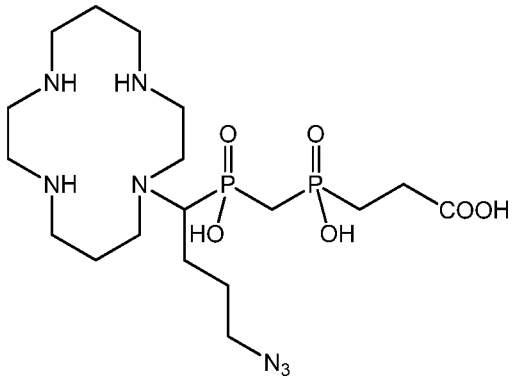
several times co-evaporated with water. The crude product was purified by preparative HPLC (C8; H_2O–0.1 % TFA–MeCN). The fraction containing product was lyophilized. The final product was obtained as an off-yellow material (203 mg; 74 %; 1 step; based on **35**·5.5H_2O).

NMR (D_2O): **^{1}H** δ 1.73 (CH_2—CH_2—CH_2, m, 1H); 1.79 (CH_2—CH_2—CH_2, m, 1H); 2.08 (P—CH_2—P, m, 2H); 2.33 (CH_2—CH_2—CH_2, m, 1H); 2.38 (CH_2—CH_2—CH_2, m, 1H); 2.63 (*cycle*, bm, 4H); 2.82–3.01 (*cycle*, bm, 5H); 3.07–3.35 (*cycle*, P—CH_2—C, N—CH_2—P, bm, 13H); 3.42–3.57 (*cycle*, N—CH_2—P bm, 4H); 3.62–3.83 (*cycle*, N—CH_2—P, bm, 4H); 4.11 (CH_2—N—CH_2, s, 4H), 7.44 (*arom.*, m, 6H); 7.96 (*arom.*, t, 2H, $^2J_{HH}$ = 8 Hz); 8.23 (C*H*—C—N, d, 2H, $^2J_{HH}$ = 8 Hz); 8.40 (*arom.*, dm, 2H, $^2J_{HH}$ = 6 Hz); **^{13}C**{^{1}H} δ 19.2 (CH_2—*C*H_2—CH_2, s); 20.7 (CH_2—*C*H_2—CH_2, s); 33.2 (P—*C*H_2—P, dd, $^1J_{CP}$ = 85 Hz, $^1J_{CP}$ = 81 Hz); 40.8 (P—*C*H_2—C, d, $^1J_{CP}$ = 86 Hz); 42.4 (*cycle*, s); 48.2 (*cycle*, s); 49.5 (*cycle*, s); 50.0 (*cycle*, s); 52.6 (*cycle*, d, $^3J_{CP}$ = 7 Hz); 54.2 (*cycle*, s); 55.5 (P—*C*H_2—N, d, $^1J_{CP}$ = 90 Hz); 57.2 (P—*C*H_2—N, d, $^1J_{CP}$ = 97 Hz); 57.5 (P—*C*H_2—N, d, $^1J_{CP}$ = 106 Hz); 59.1 (*cycle*, s); 59.7 (*cycle*, s); 60.2 (*cycle*, s); 60.7 (*C*H_2—N— *C*H_2, s, 4H); 123.8 (*C*H—C—N, s); 125.3 (*arom.*, s); 126.9 (*arom.*, s); 130.8 (*C*H—C—CH_2, d, $^3J_{CP}$ = 5 Hz); 142.7 (*arom.*, s); 144.0 (CH—*C*—CH_2, d, $^2J_{CP}$ = 8 Hz); 145.4 (*arom.*, s); 147.0 (*arom.*, s); 155.3 (*arom.*, s); **^{31}P**{^{1}H} δ 24.8 (CH_2—*P*—CH_2, d, 1P, $^2J_{PP}$ = 10 Hz); 30.8 (CH_2—*P*—CH_2, bs, 1P), 33.1 (CH_2—*P*—CH_2, s, 1P);

MS: (−) 805.2 [M−H$^+$]$^-$. (+) 807.3 [M+H$^+$]$^+$; 829.3 [M+Na$^+$]$^+$; 845.3 [M+K$^+$]$^+$; 851.3 [M−H$^+$+2Na$^+$]$^+$.

EA ($C_{35}H_{53}N_8O_8P_3$·2TFA·H_2O, M_R = 1052.8): C 44.5 (44.5); H 5.5 (5.4); N 10.6 (10.4).

Example 78: *Synthesis of compound* ***56***



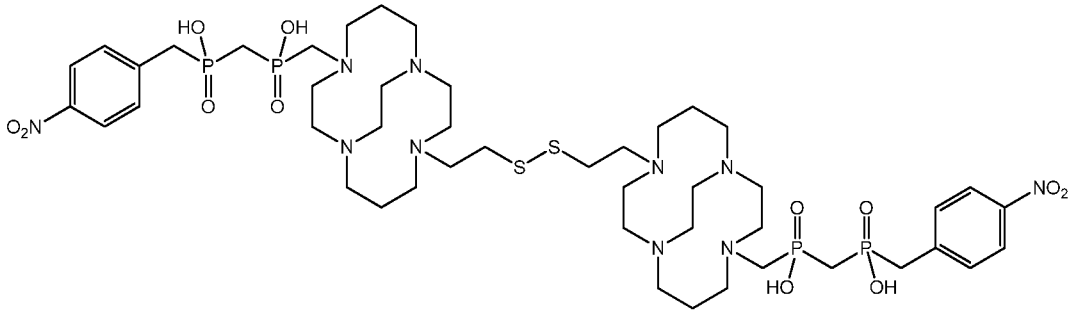
Into a glass vial (20 mL), 1,4,8,11-tetraazacyclotetradecane (463 mg; 2.31 mmol; 4.0 equiv.) was weighted, and, compound **D** (224 mg; 1.04 mmol; 1.8 equiv.), 4-azido-butanal (64.8 mg; 573 μmol; 1.0 equiv.), and aqueous HCl (6 M; 5 mL) were consecutively added. The suspension was stirred at 60 °C overnight. On next day, the reaction mixture was evaporated to dryness and the residue was several times co-evaporated with water. The crude product was purified by ion exchange resin chromatography (DOWEX 50; H^+-form; $H_2O \rightarrow$ 10 % aqueous pyridine). The pyridine fraction containing product was evaporated to dryness and the residue was several times co-evaporated with water. Subsequently, the crude product was purified by preparative HPLC (C8; H_2O–0.1 % TFA–MeCN). The fraction containing product was lyophilized. The final product was obtained as a white material (212 mg; 70 %; 1 step; based on 4-azido-butanal).

NMR (D_2O): **^{1}H** δ 1.52 (C*H*$_2$—N_3, t, 2H, $^3J_{HH}$ = 7 Hz); 1.65–2.28 (P—C*H*$_2$—P, C*H*$_2$, *cycle*, bm, 12H); 2.44–3.52 (*cycle*, bm, 19H); **^{13}C**{^{1}H} δ 19.8 (*C*H$_2$, s); 22.8 (*cycle*, s); 24.4 (*C*H$_2$, s); 26.5 (*cycle*, s); 28.2 (P—*C*H$_2$—C, d, $^1J_{CP}$ = 93 Hz); 30.3 (*C*H$_2$—CO, s); 34.2 (P—*C*H$_2$—P, t, $^1J_{CP}$ = 76 Hz); 44.2 (*cycle*, s); 45.3 (*cycle*, s); 46.8 (*cycle*, s); 47.0 (*cycle*, s); 49.5 (*cycle*, s); 49.8 (*cycle*, d, $^3J_{CP}$ = 12 Hz); 50.0 (*cycle*, s); 50.5 (*cycle*, s); 52.2 (*C*H$_2$—N_3, s); 53.1 (N—*C*H—P, d, $^1J_{CP}$ = 109 Hz); 177.2 (*C*O, d, $^3J_{CP}$ = 14 Hz); **^{31}P**{^{1}H} δ 28.4 (*P*—CH$_2$—C, d, 1P, $^2J_{PH}$ = 12 Hz); 34.4 (N—CH—*P*, m, 1P).

MS: (−) 492.2 [M−(H$_3$O)$^+$]$^-$; 510.2 [M−H$^+$]$^-$.

EA ($C_{18}H_{39}N_7O_6P_2 \cdot H_2O$, M_R = 529.5): C 40.8 (50.0); H 7.8 (7.7); N 18.5 (18.6).

Example 79: *Synthesis of compound* ***57***



Into a glass vial (20 mL), 35·5.5H_2O (145 mg; 235 μmol; 4.0 equiv.) and bis(2-bromoethyl)disulphide (16.5 mg; 59 μmol; 1.0 equiv.) were weighted, and dry MeCN (10 mL) and anhydrous K_2CO_3 (163 mg; 1.18 mmol; 20 equiv.) were consecutively added. The mixture was stirred at room temperature for 5 days. Subsequently, the

mixture was filtered through syringe filter (Millipore; 0.22 μm). The filtrate was purified by preparative HPLC (C8; H_2O–0.1% TFA–MeCN). The fraction containing product was lyophilized. The final product was obtained as an off-yellow material (58.5 mg; 69 %, 1 step, based on bis(2-bromoethyl)disulphide).

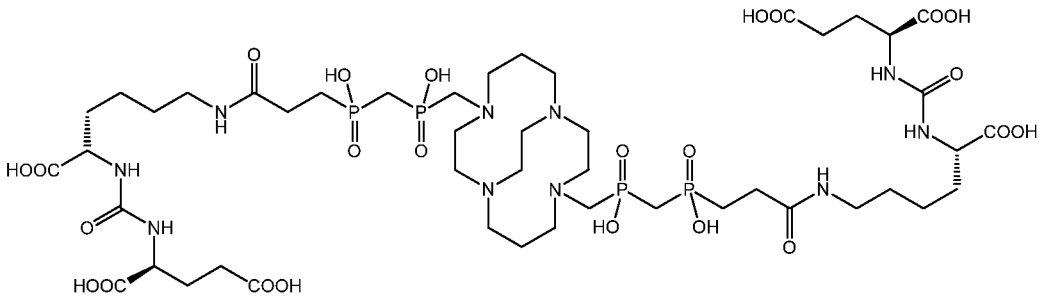
$^{31}P\{^1H\}$ δ 30.4 (CH_2—*P*—CH_2, bm, 2P); 33.2 (CH_2—*P*—CH_2, m, 2P).

MS: (–) 1173.5 $[M–2H^+ + Na^+]^-$. (+) 1152.6 $[M+H^+]^+$+ 1175.7 $[M+Na^+]^+$; 1191.6 $[M+K^+]^+$; 1197.6 $[M–H^+ + 2Na^+]^+$; 1219.7 $[M–2H^+ + 3Na^+]^+$.

EA ($C_{46}H_{80}N_{10}O_{12}P_4S \cdot 2TFA \cdot 3H_2O$, M_R = 1435.3): C 41.8 (41.4); H 6.2 (5.9); N 9.8 (9.6).

Disulphidic (oxidized) form of thiols is a stable form suitable for storage and the thiol group could be easily generated from them by *in-situ* reaction with mild reductive agents as tris(2-carboxyethyl)phosphine (TCEP).

Example 80: *Conjugate of compound* ***35*** *with a compound targeting the PSMA receptor*



Into a glass vial, compound **35**·$2H_2O$ (79.0 mg; 110 μmol; 1.0 equiv.) was weighted. The following reagents were added in the consecutive order: (*S*)-di-*t*-butyl 2-{3-[(*S*)-6-amino-1-*t*-butoxy-1-oxohexan-2-yl]ureido}pentanedioate (prepared according to R. P. Murelli et al. *J. Am. Chem. Soc.* 2009, **131**, 17090–17092; 108 mg; 220 μmol; 2.2 equiv.), dry DMSO (2 mL), *N*,*N*-diisopropylethylamine (96 μL; 550 μmol; 5.0 equiv.) and TBTU (142 mg; 442 μmol; 4.0 equiv.). After stirring at room temperature for 30 min, another *N*,*N*-diisopropylethylamine (96 μL; 550 μmol; 5.0 equiv.) and TBTU (142 mg; 442 μmol; 4.0 equiv.) were added. After stirring for further 30 min, the mixture was directly purified by preparative HPLC (C8; gradient elution H_2O–0.1 % TFA–MeCN). The fraction containing product was evaporated to dryness. The residue was dissolved in trifluoroacetic acid (2 mL) and the solution was stirred room temperature overnight. Then, the mixture was evaporated to dryness and

co-evaporated with water several times. The residue was dissolved in water (50 mL) and lyophilized. The final product was obtained as a white material (79.2 mg; 54 %; based on **35**·2H_2O).

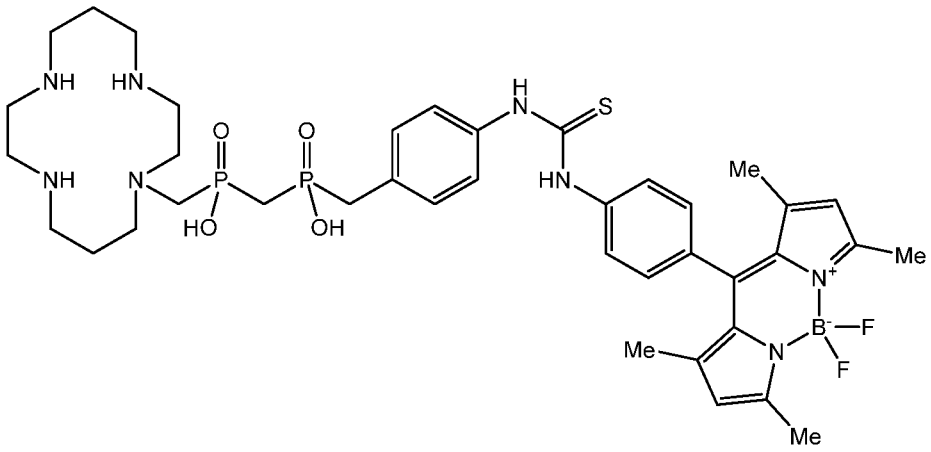
NMR (D_2O): **^{1}H** δ 1.45 (CH_2, m, 4H); 1.57 (CH_2, p, 4H, $^3J_{HH}$ = 5 Hz); 1.68 (CH_2, m, 4H); 1.76–2.33 (*cycle*, CH_2, P—CH_2—C bm, 10H); 2.39 (CH_2—CO, t, 4H, $^3J_{HH}$ = 8 Hz); 2.61–3.92 (*cycle*, CH_2—*N*—CO, N—CH_2—P, bm, 28H); 4.36 (C*H*, t, 2H, $^3J_{HH}$ = 7 Hz); 4.52 (C*H*, t, 2H, $^3J_{HH}$ = 6 Hz); **^{31}P**{^{1}H} δ 28.3 (CH_2—*P*—CH_2, bm, 2P); 36.0 (CH_2—*P*—CH_2, m, 2P).

MS: (–) 1284.2 [M–H^+]$^-$. (+) 1286.5 [M+H^+]$^+$; 1307.0 [M+Na^+]$^+$; 1323.3 [M+K^+]$^+$.

EA ($C_{46}H_{84}N_{10}O_{24}P_4$·2.5$H_2O$, M_R = 1330.1): C 41.0 (41.4); H 6.9 (6,7); N 10.1 (10.5).

The conjugates with other PSMA inhibitors, based on urea derivatives or on organophosphorus acids, can be obtained analogously.

Example 81: *Conjugate of compound **9** with a fluorescence label, BODIPY*

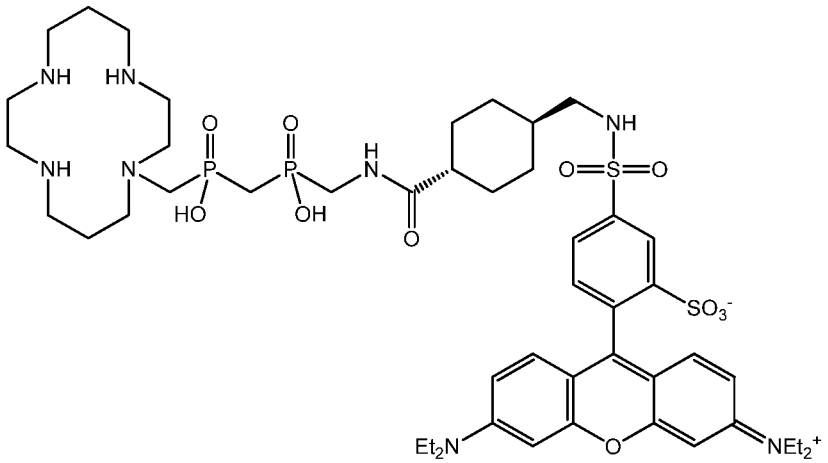


Into a glass vial, **9**·3H_2O (21.7 mg; 42.1 μmol; 2.5 equiv.) and –NCS derivative of phenyl-BODIPY (6.4 mg; 16.8 μmol; 1.0 equiv.) were weighted out and MeCN (250 μL) and aqueous buffer solution (MOPS-NaOH; 0.3 M; pH 8, 550 μL) were consecutively added. The mixture was stirred at room temperature overnight. Subsequently, the mixture was directly purified by preparative HPLC (C8; H_2O–0.1% TFA–MeCN). The fraction containing product was lyophilized. The final product was obtained as an orange material (10.3 mg; 73 %, 1 step, based on NCS derivative of bodipy).

NMR (D_2O): **^{31}P**{^{1}H} δ 30.1 (*P*—CH_2—N, m, 1P); 31.8 (*P*—CH_2—N, s, 1P).

MS: (–) 841.2 [M–H^+]$^-$; (+) 843.3 [M+H^+]$^+$; 865.3 [M+Na^+]$^+$; 881.4 [M+K^+]$^+$.

Example 82: *Conjugate of compound* ***13*** *with rhodamine*

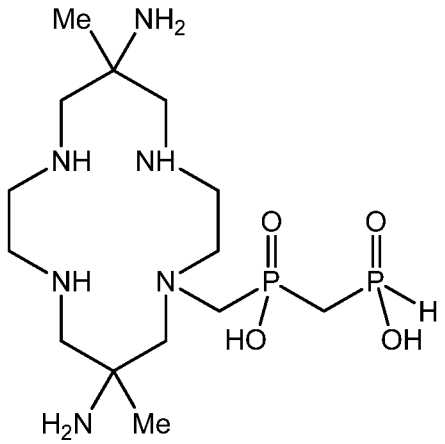


Into a glass vial, **13**·2.5H_2O (10.1 mg; 24.5 μmol; 2.1 equiv.) and *N*-[*trans*-4-(succinimidyloxycarbonyl)cyclohexylmethyl]sulfonamid-disulforhodaminu B (9.3 mg; 11.7 μmol; 1.0 equiv.) were weighted out and MeCN (500 μL) and aqueous buffer solution (MES-NaOH; 0.5 M; pH 7, 500 μL) were consecutively added. The mixture was stirred at room temperature two days. Subsequently, the mixture was directly purified by preparative HPLC (C8; H_2O–0.1% TFA–MeCN). The fraction containing product was lyophilized. The final product was obtained as a pink material (5.2 mg; 45%, 1 step, based on NCS ester of rhodamine B).

NMR (D_2O): ^{31}**P**{^{1}H} δ 29.8 (*P*—CH_2—N, bm, 1P); 36.2 (*P*—CH_2—N, m, 1P).

MS: (+) 993.5 $[M+H^+]^+$; 1015.4 $[M+Na^+]^+$.

Example 83: *Synthesis of compound* ***58***



Into a glass vial (4 mL), compound **16**·3HCl·H_2O (48.3 mg; 80.3 μmol) was weighted out. Consequently, aqueous HCl (1 M; 2 mL) and zinc powder (ca. 100 mg)

were added. The suspension was stirred at room temperature for 3 h. Subsequently, the mixture was filtered through syringe filter (Millipore; 0.22 μm). The filtrate was evaporated to dryness and the residue was dissolved in water (0.5 mL). Then, aqueous HCl (12 M; 1.5 mL) and *i*PrOH (2 mL) were added. The next day, the precipitate was centrifugated. The supernatant was decanted out the solid material was centrifugated with *i*PrOH (2×2 mL) and Et_2O (1×2 mL). The product was dried in vacuum desiccator. The final product was obtained as a white material (26.6 mg; 54 %, 1 step, based on **16**·3HCl·H_2O).

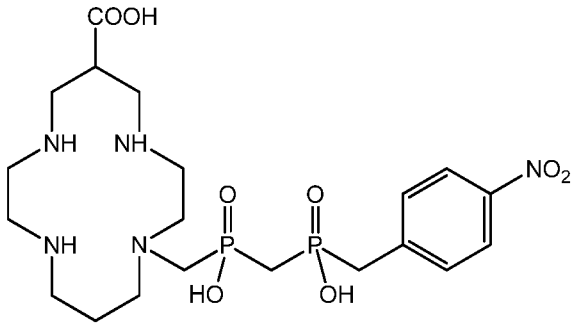
NMR (D_2O): **^{1}H** δ 1.82 (C*H*$_3$, s, 3H); 1.97 (C*H*$_3$, s, 3H); 2.15 (P—C*H*$_2$—P, dd, 2H, $^2J_{HP}$ = 18 Hz, $^2J_{HP}$ = 16 Hz); 2.64–3.34 (*cycle*, N—C*H*$_2$—P m, 18H); 7.13 (P*H*, d, 1H, $^1J_{HP}$ = 528 Hz); **^{13}C**{^{1}H} δ 23.9 (*C*H$_3$, s); 25.3 (*C*H$_3$, s); 34.9 (P—*C*H$_2$—P, dd, $^1J_{CP}$ = 80 Hz, $^1J_{CP}$ = 76 Hz); 48.0 (*cycle*, s); 48.7 (*cycle*, s); 48.9 (*cycle*, s); 50.3 (*cycle*, s); 51.3 (*cycle*, s); 51.8 (*cycle*, s); 55.3 (*cycle*, s); 57.9 (*C*—NH$_2$, s); 58.2 (N—*C*H$_2$—P, d, $^1J_{CP}$ = 101 Hz); 58.4 (*C*—NH$_2$, s); 59.3 (*cycle*, d, $^3J_{CP}$ = 10 Hz); **^{31}P** δ 19.8 (*P*H, dt, 1P, $^1J_{PH}$ = 528 Hz, $^2J_{PH}$ = 18 Hz); 33.7 (N—CH$_2$—*P*, m, 1P).

MS: (−) 413.2 [M−H$^+$]$^-$. (+) 415.3 [M+H$^+$]$^+$; 437.3 [M+Na$^+$]$^+$.

TLC (SiO_2, EtOH–conc. aq. NH_4OH 1:1): R_f = 0.4.

EA ($C_{14}H_{36}N_6O_4P_2$·5HCl·H_2O, M_R = 614.7): C 27.4 (27.2); H 7.1 (7.2); N 13.7 (14.0).

Example 84: *Synthesis of compound* ***59***



Into a glass vial (4 mL), tetrahydrochloride of 1,4,8,11-tetrazacyclotetradecane-6-carboxylic acid (388 mg; 994 μmol; 3.0 equiv.), compound **B** (135 mg; 484 μmol; 1.5 equiv.) and paraformaldehyde (9.8 mg; 327 μmol; 1.0 equiv.) were weighted, and aqueous HCl (6 M; 1 mL) and trifluoroacetic acid (1 mL) were added. The mixture was stirred at 60 °C for three days. The solution was evaporated to dryness and the residue was co-evaporated with water several times. The crude product was purified by preparative HPLC (C8; H_2O–0.1% TFA–MeCN). The fraction containing product

was lyophilized. The final product was obtained as a white material (49.7 mg; 24 %, 1 step, based on paraformaldehyde).

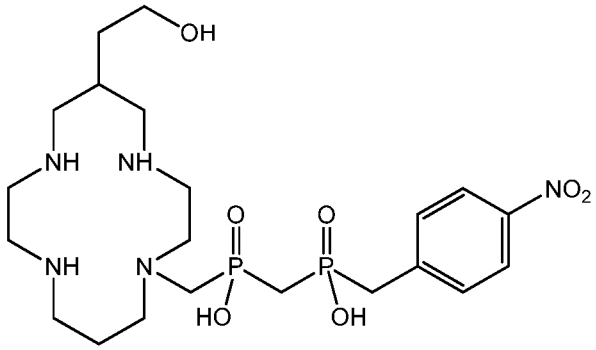
NMR (D_2O): **^{1}H** δ 1.77 (*cycle*, p, 2H, $^3J_{HH}$ = 4 Hz); 2.01 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 17 Hz); 2.33–2.99 (*cycle*, N—CH_2—P, m, 19H); 3.25 (CH_2—C—CH, d, 2H, $^2J_{HP}$ = 16 Hz); 7.61 (C*H*—C—CH_2, d, 2H, $^2J_{HH}$ = 8 Hz); 8.27 (C*H*—C—N, d, 2H, $^2J_{HH}$ = 8 Hz); **^{31}P**{^{1}H} δ 30.1 (CH_2—*P*—CH_2, d, 1P, $^2J_{PP}$ = 11 Hz); 32.8 (CH_2—*P*—CH_2, d, 1P, $^2J_{PP}$ = 11 Hz).

MS: (−) 515.9 $[M+H^+]^+$; 534.0 $[M+H^+]^+$. (+) 336.0 $[M+H^+]^+$.

TLC (SiO_2, EtOH–conc. aq. NH_4OH 1:1): R_f = 0.5.

EA ($C_{20}H_{35}N_6O_8P_2 \cdot 0.5TFA \cdot 2H_2O$, M_R = 667.6): C 40.1 (39.9); H 6.3 (6.6); N 11.1 (10.8).

Example 85: *Synthesis of compound* ***60***



Into a glass vial (4 mL), 2-(1,4,8,11-tetrazacyclotetradecan-6-yl)ethanol hydrate (prepared according to N. Camus *et al. RSC Adv.* 2015, **5**, 85898–85910; 157 mg; 598 μmol; 4.0 equiv.), compound **B** (97 mg; 348 μmol; 2.3 equiv.) and paraformaldehyde (4.5 mg; 150 μmol; 1.0 equiv.) were weighted, and aqueous HCl (12 M; 1 mL) was added. The mixture was stirred at 60 °C for two days. Consequently, water was added just to dissolve all solids. The solution was evaporated to dryness and the residue was co-evaporated with water several times. The crude product was purified by preparative HPLC (C8; H_2O–0.1% TFA–MeCN). The fraction containing product was lyophilized. The final product was obtained as an off-yellow material (22.4 mg; 22 %, 1 step, based on paraformaldehyde).

NMR (D_2O): **^{1}H** δ 1.68–1.75 (*cycle*, CH_2—CH_2—O, bm, 4H); 2.01 (P—CH_2—P, dd, 2H, $^2J_{HP}$ = 17 Hz, $^2J_{HP}$ = 15 Hz); 2.13 (*cycle*, m, 1H); 2.48–3.13 (*cycle*, N—CH_2—P, m, 18H); 3.32 (CH_2—C—CH, d, 2H, $^2J_{HP}$ = 16 Hz); 3.65 (CH_2—OH, t, $^3J_{HH}$ = 9 Hz);

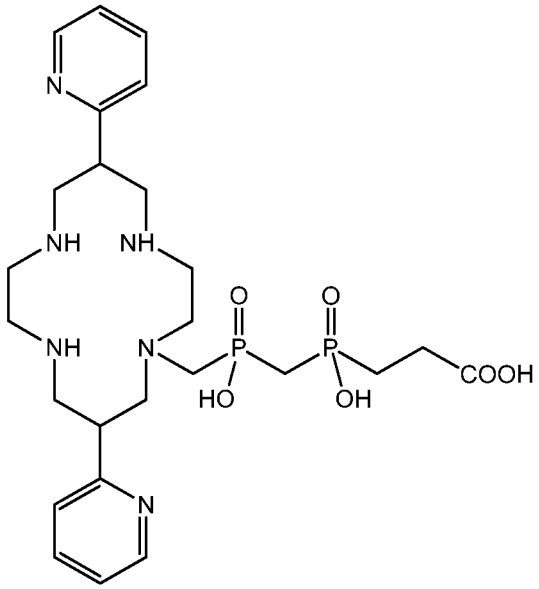
7.58 (C*H*—C—CH_2, d, 2H, $^2J_{HH}$ = 9 Hz); 8.17 (C*H*—C—N, d, 2H, $^2J_{HH}$ = 9 Hz); **^{13}C**{^{1}H} δ 24.9 (CH_2—*C*H_2—CH_2, s); 31.3 (CH_2—*C*H—CH_2, s); 32.9 (*C*H_2—CH_2—O, s); 34.2 (P—*C*H_2—P, dd, $^1J_{CP}$ = 82 Hz, $^1J_{CP}$ = 79 Hz); 40.5 (P—*C*H_2—C, d, $^1J_{CP}$ = 86 Hz); 44.1 (*cycle*, s); 45.0 (*cycle*, s); 45.6 (*cycle*, s); 45.9 (*cycle*, s); 46.2 (*cycle*, s); 47.1 (*cycle*, s); 55.1 (*cycle*, s); 55.2 (*cycle*, s); 58.3 (P—*C*H_2—N, d, $^1J_{CP}$ = 107 Hz); 62.4 (*C*H_2—OH, s); 125.6 (*C*H—C—N, s); 129.9 (*C*H—C—CH_2, d, $^3J_{CP}$ = 5 Hz); 142.3 (CH—*C*—CH_2, s); 147.1 (CH—*C*—N, s); **^{31}P**{^{1}H} δ 28.5 (CH_2—*P*—CH_2, d, 1P, $^2J_{PP}$ = 10 Hz); 34.3 (CH_2—*P*—CH_2, d, 1P, $^2J_{PP}$ = 10 Hz).

MS: (−) 534.2 [M−H$^+$]$^-$. (+) 536.2 [M+H$^+$]$^+$; 558.2 [M+Na$^+$]$^+$; 574.2 [M+K$^+$]$^+$.

TLC (SiO_2, *i*PrOH–conc. aq. NH_4OH–H_2O 7:3:3): R_f = 0.6.

EA ($C_{21}H_{39}N_5O_7P_2$·TFA·H_2O, M_R = 667.6): C 41.4 (41.7); H 6.3 (5.9); N 10.5 (10.3).

Example 86: *Synthesis of compound* ***61***



Into a glass vial (20 mL), tetrahydroperchlorate 6,13-di(2-pyridyl)-1,4,8,11-tetrazacyclotetradecane dihydrate (synthesized according to P. Comba et al. *Inorg. Chem.* 2001, **40**, 2335–2345; 1.11 g; 1.40 mmol; 3.3 equiv.), compound **D** (128 mg; 592 μmol; 1.4 equiv.) and paraformaldehyde (12.7 mg; 423 μmol; 1.0 equiv.) were weighted, and aqueous HCl (12 M; 5 mL) was added. The mixture was stirred at 50 °C for two days. The reaction mixture was evaporated to dryness and the residue was co-evaporated with water several times. The crude product was purified by ion exchange chromatography (DOWEX 50; H$^+$-form, H_2O → 10 % aq. pyridine). The pyridine fraction containing product was evaporated to dryness and the the residue was co-evaporated with water

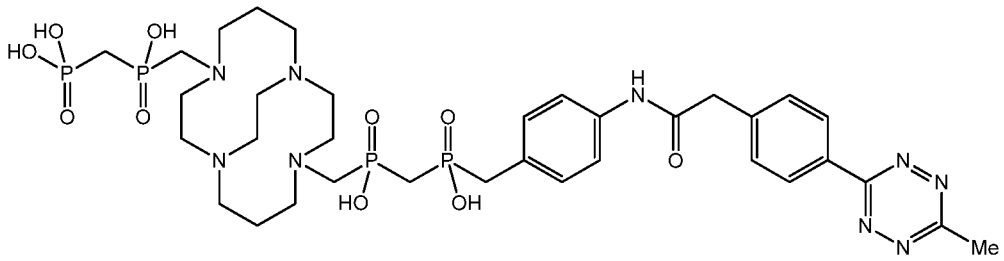
several times. The residue was then dried by vacuum pump obtained and further drying was accomplished with desiccator over P_2O_5. The final product was obtained as an off-yellow material (184 mg; 66 %, 1 step, based on paraformaldehyde).

NMR (D_2O): **^{1}H** δ 1.98 (P—CH_2—C, m, 2H); 2.08 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 17 Hz); 2.41 (CH_2—CO, m, 2H); 2.63–2.89 (*cycle*, N—CH_2—P, CH_2—C*H*—CH_2, m, 20H); 7.48 (*arom.*, m, 4H); 7.66 (*arom.*, dd, 2H, $^3J_{HH}$ = 8 Hz, $^3J_{HH}$ = 6 Hz); 8.38 (*arom.*, dm, 2H, $^3J_{HH}$ = 6 Hz); **^{13}C**{^{1}H} δ 29.5 (P—*C*H_2—C, d, $^1J_{CP}$ = 95 Hz); 31.6 (*C*H_2—CO, s); 34.0 (P—*C*H_2—P, t, $^1J_{CP}$ = 81 Hz); 40.3 (CH_2—*C*H—CH_2, s); 41.5 (CH_2—*C*H—CH_2, s); 44.0 (*cycle*, s); 46.5 (*cycle*, s); 46.9 (*cycle*, s); 47.2 (*cycle*, s); 47.8 (*cycle*, s); 50.3 (*cycle*, s); 54.5 (*cycle*, s); 55.1 (N—*C*H_2—P, d, $^1J_{CP}$ = 109 Hz); 55.8 (*cycle*, s); 124.9 (*arom.*, s); 125.3 (*arom.*, s); 127.4 (*arom.*, s); 131.6 (*arom.*, s); 162.0 (*arom.*, s); 182.6 (*C*O, d, $^3J_{CP}$ = 17 Hz); **^{31}P**{^{1}H} δ 32.2 (*P*—CH_2—N, d, 1P, $^2J_{PP}$ = 11 Hz); 37.8 (*P*—CH_2—CH_2, d, 1P, $^2J_{PP}$ = 11 Hz).

MS: (−) 563.1 $[M-H^+]^-$; 581.0 $[M-H^+]^-$. (+) 583.2 $[M+H^+]^+$; 605.1 $[M+Na^+]^+$; 621.1 $[M+K^+]^+$.

EA ($C_{25}H_{40}N_6O_6P_2 \cdot 4H_2O$, M_R = 654.6): C 45.9 (46.1); H 7.4 (7.3); N 12.8 (13.0).

Example 87: *Synthesis of conjugate of compound* ***38*** *with tetrazine*



Into a glass vial (4 mL), compound **38**·4H_2O (33.3 mg; 45.5 μmol; 1.0 equiv.) and NHS ester of 2-(4-(6-methyl-1,2,4,5-tetrazin-3-yl)phenyl)acetic acid (16.4 mg; 50.1 μmol; 1.1 equiv.) were weighted, and aqueous buffer MES/NaOH (1.0 M; pH 6.2, 1.5 mL) and MeCN (1,5 mL) were added. The mixture was stirred at room temperature for two days. Consequently, water was then directly purified by preparative HPLC (C8; H_2O–0.1% TFA–MeCN). The fraction containing product was lyophilized. The final product was obtained as a pink material (19.2 mg; 43 %, 1 step, based on **38**·4H_2O).

NMR (D_2O): **^{1}H** δ 1.97 (*cycle*, bm, 2H); 2.26 (*cycle*, bm, 2H); 2.31 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 16 Hz); 2.36 (P—CH_2—P, t, 2H, $^2J_{HP}$ = 19 Hz); 2.71–3,86 (*cycle*, N—CH_2—P, P—CH_2—C, CH_3, bm, 29H); 3.93 (CH_2—CO, s, 2H); 7.38 (C*H*, d, 2H, $^3J_{HH}$

= 8 Hz); 7.46 (C*H*, d, 2H, $^{3}J_{HH}$ = 8 Hz); 7.67 (C*H*, d, 2H, $^{3}J_{HH}$ = 8 Hz); 8.43 (C*H*, d, 2H, $^{3}J_{HH}$ = 8 Hz); **^{13}C**{^{1}H} 20.4 (CH_2—*C*H_2—CH_2, bm); 20.6 (CH_2—*C*H_2—CH_2, s); 20.7 (*C*H_3, s); 32.8 (2 × P—*C*H_2—P, m); 38.6 (P—*C*H_2—C, d, $^{1}J_{CP}$ = 91 Hz); 43.6 (*C*H_2—*C*O, s); 47.4–58.7 (12 × N—*C*H_2, bm); 126.7 (*C*H—C—N, s); 130.1 (CH—*C*—N, s); 131.8 (*C*H—C—CH_2, s); 132.2 (CH—*C*—CH_2, d, $^{2}J_{CP}$ = 8 Hz); 164.7 (N—*C*—N, s); 167.9 (N—*C*—N, s); 173.2 (*C*O, s); **^{31}P**{^{1}H} δ 16.0 (HO—*P*—OH, m, 1P); 22.5 (*P*—CH_2—N, bm, 1P); 23.5 (*P*—CH_2—N, bm, 1P); 38.8 (*P*—CH_2—C, m, 1P).

MS: (−) 870.3 $[M-H^+]^-$. (+) 872.5 $[M+H^+]^+$; 894.5 $[M+Na^+]^+$; 910.5 $[M+K^+]^+$.

TLC (SiO_2, *i*PrOH–conc. aq. NH_4OH–H_2O 7:3:3): R_f = 0.4.

EA ($C_{34}H_{53}N_9O_{10}P_4$·TFA, M_R = 985.8): C 43.9 (43.8); H 5.5 (5.3); N 12.8 (13.1).

Example 88: *Conjugation of compound **15** to copolymer containing poly(acrylamide)*

Block copolymer of poly[*N*-(2-hydroxopropyl)methakrylamide and poly-L-lysine (ten L-Lys residues) was obtained according to K. Tappertzhofen et al. *Macromolec. Biosci.* 2015, **15**, 1159–1173 (average M_w 14 kDa, one poly-L-Lys chain per the co-polymer). Compound **15** (93 mg; 135 μmol; 1.5 equiv. per an amino group) and *N*-hydroxysuccinimide (NHS; 15.5 mg; 135 μmol; 1.5 equiv.) were dissolved in aqueous MES/NaOH buffer (pH 5.5; 0.5 M; 2 mL). Subsequently, a DMSO/H_2O 1:1 (3.0 mL) solution containing 140 mg (cca 90 μmol of amino groups; 1 equiv.) of the polymer was added. To this solution, solid EDC·HCl (26 mg; 135 μmol; 1.5 equiv.) was added and the mixture was stirred at room temperature for 2 days. Then, the reaction mixture was concentrated to 2 mL and the solution was filtered through a syringe filter (Millipore; 0.22 μm) into ultrafiltration cell. Ultrafiltration (pressure 3 atm) on 3-kDa membrane was carried out three times from 50 mL to 10 mL of the retenate and it was followed by continuous ultrafiltration (pressure 4 atm) until 1000 mL of eluate was obtained. The retenate was lyophilized to give a white solid (175 mg). An average ligand number bound to the polymer was determined (^{1}H NMR spectrum) to be ca. 8.0

Example 89 *Conjugate of compound **39** and poly(acrylamide) with free amino groups*

Poly[*N*-(2-hydroxopropyl)methakrylamide with free amino groups was prepared the polymer active ester consecutive reactions, first with NH_2-$(CH_2)_6$NH-C(O)CH_2NHBoc and later with 2-hydroxopropylaminem, which were followed by Boc protecting group removal, according to L. Nuhn et al. *Angew. Chem. Int. Ed.* 2013, **52**,

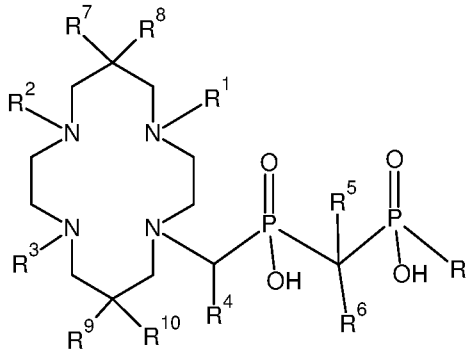
10652–10656 (average M_w 16 kDa, ca. 22 free amino groups per molecule). A buffer MOPS/NaOH (5 mL, pH 7.5, 0.5 M) solution was added to the polymer with free glycine amino groups (105 mg, ca. 140 μmol amino groups) and the compound **39** (111 mg; 140 μmol, equivalent amount to a number of the amine groups) and the solution was stirred at room temperature for 12 h.. The solution was filtered through a syringe filter (Millipore; 0.22 μm) into ultrafiltration cell. Ultrafiltration (pressure 3 atm) on 3-kDa membrane was carried out three times from 50 mL to 10 mL of the retenate and it was followed by continuous ultrafiltration (pressure 4 atm) until 1000 mL of eluate was obtained. The retenate was lyophilized to give a white solid (185 mg). An average ligand number bound to the polymer was determined (^{1}H NMR spectrum) to be 19.6

Example 90 *Conjugate of compound **57** and poly(acrylamide) through thiol coupling*

Poly[*N*-(2-hydroxopropyl)methakrylamide with free maleimide groups was prepared the polymer active ester by consecutive reactions, first with aminohexamethylene-maleimide and later with 2-hydroxopropylaminem according to L. Nuhn et al. *Angew. Chem. Int. Ed.* 2013, **52**, 10652–10656 (average M_w 18 kDa, ca. 19 free maleimide groups per polymer). Polymer (115 mg, ca. 120 μmol maleimide groups) was dissolved in aqueous buffer MOPS/NaOH (5 mL; 0.5 M, pH 7.5) and compound **57** (86 mg; 60 μmol) was added, i.e. equivalent amount of –SH groups per a number of reactive groups per polymer was used. The solution was bubbled with argon (10 min). Free –SH group was generated *in-situ* after addition of tris(2-karboxyethyl)phosphine hydrochloride (TCEP·HCl, 17 mg, 60 μmol) in the argon flow and the mixture was stirred with no air access for 12 h. In the argon flow, compound **57** (43 mg; 30 μmol, i.e. ca. 0.5 molar equivalent with regard to a number of reactive groups on the polymer) dissolved in aqueous buffer (2 mL; 0.1 M, pH 7.5) was added, it was followed by addition of TCEP·HCl (11 mg, cca 35 μmol) and the mixture was stirred with no air access for 12 h. The solution was filtered through a syringe filter (Millipore; 0.22 μm) into ultrafiltration cell. Ultrafiltration (pressure 3 atm) on 3-kDa membrane was carried out three times from 50 mL to 10 mL of the retenate and it was followed by continuous ultrafiltration (pressure 4 atm) until 900 mL of eluate was obtained. The retenate was lyophilized to give a white solid (185 mg). An average ligand number bound to the polymer was determined (^{1}H NMR spectrum) to be 16.5

CLAIMS

1. Cyclam based compounds of the general formula **(I)**



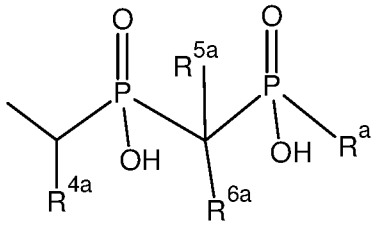
(I)

wherein

R, R^a, R^1, R^2, R^3 are independently selected from the group comprising

H, OH, (C1 to C6)alkyl, which may be linear or branched, (C3 to C6)cycloalkyl, benzyl,

and/or R^1 and/or R^2 and/or R^3 is a bis-phosphorus acid of the general formula **(II)**

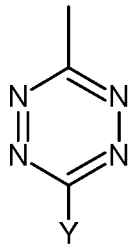


(II)

and/or R^1 and R^3 together form (C2 to C3)alkylene, which may be substituted with one or more linear or branched (C1 to C6)alkyls,

and/or R, R^a are independently selected from phenyl and (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O,

wherein the (C1 to C6)alkyl, (C3 to C6)cycloalkyl, phenyl, benzyl and (C5 to C6) heterocycle, containing at least one heteroatom of N, S, O, may be independently substituted with one or more groups selected from COOH; NH_2; NO_2, NX_2; $C(O)NX_2$; NHX; C(O)NHX; OH; SH; -NCS; tetrazine of the general formula **(III)**;



(III)

(C7 to C8)cycloalkenyl in *trans* configuration, which may eventually be further substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; norbornenyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; $-N_3$; (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O; (C2 to C6)alkynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2,-NCS, -NCO, N_3 and SH; cyclooctynyl, eventually substituted with one or more groups chosen from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; cycloazaoctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; maleimide; phenyl; benzyl and -P(O)(OH)Z;

and wherein R^4, R^{4a}, R^5 and R^{5a} are independently H, (C1 to C6)alkyl, which may be linear or branched, (C3 to C6)cycloalkyl, benzyl;

wherein (C1 to C6)alkyl, (C3 to C6)cycloalkyl and benzyl may be independently substituted with one or more groups selected from COOH; NH_2; NO_2, NX_2; $C(O)NX_2$; NHX; C(O)NHX; OH; SH; -NCS; tetrazine of the general formula (**III**); (C7 to C8)cycloalkenyl in *trans* configuration, which may eventually be further substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; norbornenyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; $-N_3$; (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O; (C2 to C6)alkynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; cyclooctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; cycloazaoctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; maleimide; phenyl; benzyl and –P(O)(OH)Z;

and wherein R^6 and R^{6a} is H;

and wherein R^7, R^8, R^9 and R^{10} are independently selected from the group comprising H, (C1 to C6)alkyl, (C3 to C6)cycloalkyl, benzyl, phenyl, NO_2, COOH, (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O, and/or altogether R^7 and R^8 contain (C2 to C3)alkylene or vinylene and/or altogether R^9 and R^{10} contain (C2 to C3)alkylene or vinylene,

wherein (C1 to C6)alkyl, (C3 to C6)cycloalkyl, phenyl, benzyl, (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O, (C2 to C3)alkylene and vinylene may be independently substituted with a group or groups selected from COOH; NH_2; NO_2; NX_2; $C(O)NX_2$; SH; tetrazine of the general formula (**III**); (C7 to C8)cycloalkenyl in *trans* configuration, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; norbornenyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; -N_3; (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O; (C2 to C6)alkynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; cyclooctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; cycloazaoctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; maleimide; phenyl; benzyl and –P(O)(OH)Z,

wherein Y is H, (C1 to C6)alkyl, $–CH_2COOH$, (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O, or heteroaryl, containing at least one heteroatom of N, S, O, preferably Y is an atom of hydrogen, methyl or pyridyl;

wherein Z is H; OH; (C1 to C6)alkyl, which may be linear or branched; (C1 to C6)hydroxyalkyl; (C1 to C6)alkoxyl; phenyl; (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O; or benzyl, wherein phenyl, (C5 to C6)heterocycle or benzyl may eventually be substituted with one or more groups selected from COOH, NH_2, NO_2, N_3 and SH, preferably the substituent is in *para* position;

and wherein X is independently H; (C1 to C6)alkyl, which may be linear or branched; (C3 to C6)cycloalkyl; phenyl and/or benzyl;

while for X, Y and Z applies, that (C1 to C6)alkyl, (C3 to C6)cycloalkyl, phenyl and/or benzyl may be independently substituted with one or more groups selected from COOH; NH_2; NO_2, NX_2; $C(O)NX_2$; NHX; C(O)NHX;

SH; tetrazine of the general formula (**III**); (C7 to C8)cycloalkenyl in *trans* configuration, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; norbornenyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; $-N_3$; (C2 to C6)alkynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; cyclooctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; cycloazaoctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, -NCS, -NCO, N_3 and SH; maleimide; phenyl; benzyl and -P(O)(OH)Z;

wherein at least one of the groups R, R^a, R^1, R^2, R^3, R^4, R^{4a}, R^5, R^{5a}, R^6, R^{6a}, R^7, R^8, R^9 a R^{10} contains at least one of the groups -COOH; NH_2; NO_2, NX_2, NHX; C(O)NHX; N_3; SH; -NCS; tetrazine of the general formula (**III**); (C7 to C8)cycloalkenyl in *trans* configuration, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, N_3 and SH; norbornenyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, N_3 and SH; $-N_3$; (C2 to C6)alkynyl; cyclooctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, N_3 and SH; cycloazaoctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, N_3 and SH; maleimide; phenyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, N_3 and SH; benzyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, N_3 and SH; (C1 to C6)alkyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, N_3 and SH; and -P(O)(OH)Z.

2. The cyclam based compounds according to claim 1, **characterized in that** R^1 and R^3 together form (C2 to C3)alkylene, which may be substituted with (C1 to C6)alkyl, which may be linear or branched.

3. The cyclam based compounds according to claim 1, **characterized in that** R, R^a, R^1, R^2, R^3, R^4, R^{4a}, R^5, R^{5a}, R^6 and R^{6a} are independently selected from the group comprising

H; (C1 to C6)alkyl, which may be linear or branched; (C3 to C6) cycloalkyl; benzyl; phenyl; (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O;
and/or R^1 and/or R^2 and/or R^3 is the bis-phosphorus acid of the general formula **(II)**, preferably at least one of the groups R^1, R^2 and R^3 is the bis-phosphorus acid of the general formula **(II)**, most preferably R^2 is the bis-phosphorus acid of the general formula **(II)**.

4. The cyclam based compounds according to claim 1, **characterized in that** R^2 is selected from the group comprising H; (C1 to C6)alkyl, which may be linear or branched; (C3 to C6)cycloalkyl; benzyl; phenyl; (C5 to C6)heterocycle, containing at least one heteroatom of N, S, O; and bis-phosphorus acid of the general formula **(II)**.

5. The cyclam based compounds according to claim 1, **characterized in that** they are selected from the group comprising compounds of the general formula **(I)**, whose the substituents are represented in the following combinations:

Compound number	R	R^1	R^3	R^2	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}
1	H	H	H	H	CH_3	H	H	H	H	H	H
2	H	CH_3	CH_3	CH_3	CH_3	H	H	H	H	H	H
3	H	CH_3	CH_3	H	H	H	H	H	H	H	H
4	H	CH_3	CH_3	CH_3	H	H	H	H	H	H	H
5	OH	benzyl	benzyl	H	H	H	H	H	H	H	H
7	OH	H	benzyl	benzyl	H	H	H	H	H	H	H
8	*p*-nitrobenzyl	H	H	H	H	H	H	H	H	H	H
9	*p*-aminobenzyl	H	H	H	H	H	H	H	H	H	H
10	*p*-SCN-benzyl	H	H	H	H	H	H	H	H	H	H
11	*p*-azidobenzyl	H	H	H	H	H	H	H	H	H	H
12	$-CH_2N(Bz)_2$	H	H	H	H	H	H	H	H	H	H
13	$-CH_2NH_2$	H	H	H	H	H	H	H	H	H	H
14	$-(CH_2)_2COOH$	H	H	H	H	H	H	H	H	H	H
15	H	H	H	H	H	$-(CH_2)_4COOH$	H	H	H	H	H

16	H	H	H	H	H	H	H	CH_3	NO_2	NO_2	CH_3
22	H	CH_3	CH_3	acid of formula (**II**), wherein R^a = R, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
23	$-(CH_2)_2COOH$	CH_3	CH_3	acid of formula (**II**), wherein R^a = R, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
24	OH	benzyl	benzyl	$-CH_2P(O)(OH)_2$	H	H	H	H	H	H	H
25	OH	H	H	$-CH_2P(O)(OH)_2$	H	H	H	H	H	H	H
26	OH	$-CH_2P(O)(OH)_2$	benzyl	benzyl	H	H	H	H	H	H	H
27	OH	$-CH_2P(O)(OH)_2$	H	H	H	H	H	H	H	H	H
28	H	$-(CH_2)_2-$		H	H	H	H	H	H	H	H
29	OH	$-(CH_2)_2-$		H	H	H	H	H	H	H	H
30	H	$-(CH_2)_2-$		H	CH_3	H	H	H	H	H	H
31	*p*-nitrobenzyl	$-(CH_2)_2-$		H	H	H	H	H	H	H	H
32	H	$-(CH_2)_2-$		acid of formula (**II**), wherein R^a = R, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
33	$-CH_2OH$	$-(CH_2)_2-$		acid of formula (**II**), wherein R^a = R, R^{4a} to R^{6a}	H	H	H	H	H	H	H

			= H							
34	OH	$-(CH_2)_2-$	acid of formula (**II**), wherein R^a = R, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
35	$-(CH_2)_2COOH$	$-(CH_2)_2-$	acid of formula (**II**), wherein R^a = R, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
36	H	$-(CH_2)_2-$	acid of formula (**II**), wherein R^a = OH, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
37	*p*-nitrobenzyl	$-(CH_2)_2-$	acid of formula (**II**), wherein R^a = OH, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
38	*p*-aminobenzyl	$-(CH_2)_2-$	acid of formula (**II**), wherein R^a = OH, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
39	*p*-SCN-benzyl	$-(CH_2)_2-$	acid of formula (**II**), wherein R^a = OH, R^{4a} to R^{6a} = H	H	H	H	H	H	H	H
40	*p*-azidobenzyl	$-(CH_2)_2-$	acid of formula (**II**),	H	H	H	H	H	H	H

				wherein R^a = OH, R^{4a} to R^{6a} = H							
41	*p*-nitrobenzyl	-$(CH_2)_2$-		–$CH_2P(O)(OH)(CH_2OH)$	H	H	H	H	H	H	H
42	*p*-nitrobenzyl	-$(CH_2)_2$-		–$CH_2P(O)(OH)_2$	H	H	H	H	H	H	H
43	*p*-aminobenzyl	-$(CH_2)_2$-		–$CH_2P(O)(OH)_2$	H	H	H	H	H	H	H
50	H	–$(CH_2)_2$–		H	H	–$(CH_2)_4CH_3$	H	H	H	H	H
51	H	–$(CH_2)_2$–		2-picolyl-*N*-oxide	H	–$(CH_2)_4CH_3$	H	H	H	H	H
52	H	–$(CH_2)_2$–		–CH_2COOH	H	H	H	H	H	H	H
53	OH	–$(CH_2)_2$–		–$CH_2P(O)(OH)$–$(CH_2)_2COOH$	H	H	H	H	H	H	H
54	H	–CH_3	–CH_3	–$CH_2P(O)(OH)Ph$	H	H	H	H	H	H	H
55	*p*-nitrobenzyl	–$(CH_2)_2$–		–$CH_2P(O)(OH)$–$CH_2N(2\text{-picolyl})_2$	H	H	H	H	H	H	H
56	–$(CH_2)_2COOH$	H	H	H	–$(CH_2)_3N_3$	H	H	H	H	H	H
57	*p*-nitrobenzyl	–$(CH_2)_2$–		–$(CH_2)_2S$– (dimer)	H	H	H	H	H	H	H
58	H	H	H	H	H	H	H	-CH_3	-NH_2	-NH_2	-CH_3
59	*p*-nitrobenzyl	H	H	H	H	H	H	-COOH	H	H	H
60	*p*-nitrobenzyl	H	H	H	H	H	H	-$(CH_2)_2OH$	H	H	H
61	–$(CH_2)_2COOH$	H	H	H	H	H	H	*2*-pyridyl	H	*2*-pyridyl	H

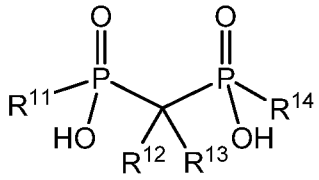
6. A conjugate of the cyclam-based compound according to any one of the preceding claims and of at least one conjugation group, which is covalently bound to the cyclam based compound, and which is selected from the group containing OH, -COOH; NH_2; NO_2, NX_2, NHX; C(O)NHX; N_3; SH; -NCS; tetrazine of the general formula (**III**); (C7 to C8)cycloalkenyl in *trans* configuration, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX; C(O)NHX; N_3 and SH; norbornenyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX; C(O)NHX; N_3 and SH; $-N_3$; (C2 to C6)alkynyl; cyclooctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX; C(O)NHX; N_3 and SH; cycloazaoctynyl, eventually substituted with one or more groups selected from COOH, NH_2, NO_2, NX_2, -NCS, -NCO, NHX, C(O)NHX, (C1 to C6)alkyl, (C6)aryl, N_3 and SH; maleimide; and -P(O)(OH)Z; wherein the conjugate may further contain a spacer between the cyclam-based compound and the conjugation group and/or between two conjugation groups, the spacer selected from the group containing (C1 to C6)*n*-alkyl, eventually substituted with C=O and/or -NH- group; phenylene; amino-acids chains with the length of 1 to 5 amino-acids; polyethylene glycols of 1 to 10 monomeric units.

7. Coordination compounds of the cyclam based compounds of the general formula (**I**) according to any one of the claims 1 to 5 or of the conjugates according to the claim 6, with metal cations selected from the group consisting of Cu^{2+}, Bi^{3+}, lanthanide(III) cations, Sc^{3+}, Y^{3+}, Pb^{2+}, Zr^{4+}, Ac^{3+}, Mn^{2+} and Mn^{3+}, preferably lanthanide(III) cations, Y^{3+} a Cu^{2+}, more preferably Lu^{3+}, Y^{3+} and Cu^{2+}.

8. A targeting conjugate, which contains the cyclam based compound of the general formula (**I**) according to any one of the claims 1 to 5 and/or the conjugate according to the claim 6 and/or the coordination compound according to the claim 7; and a targeting vector, selected from the group comprising bis(phosphonates); groups capable of fluorescence, preferably fluoresceines, rhodamines or the boron-dipyrromethene type substances; oligopeptides of 1 to 15 aminoacids; antibodies or fragments thereof, preferably the Fab fragments; folic acid; biotin; compounds targeting to PSMA receptor, preferably urea derivatives or organo-phosphorous compounds; cyclodextrins;

dendrimers; hydrophilic polymers on the basis of derivatives of acrylic acid, especially hydroxoalkylamides of acrylic acid.

9. A method of preparation of cyclam based compounds of the general formula **(I)** according to any one of the claims 1 to 5, wherein an intermediate product of the general formula **(IV)**,



(IV)

wherein R^{11}, R^{12}, R^{13} and R^{14} are in the following combinations:

Intermediate	R^{11}	R^{12}	R^{13}	R^{14}
A	H	H	H	OH
B	H	H	H	*p*-nitrobenzyl
C	H	H	H	$-CH_2N(benzyl)_2$
D	H	H	H	$-(CH_2)_2COOH$
E	H	$-(CH_2)_4COOH$	H	H
F	OH	$-(CH_2)_3NH$(4-dibenzylcyclooktynamidobutoxyl)	OH	OH

or a compound selected from the group containing methylene-bis(phosphinic acid), phosphorous acid, hydroxymethylphosphinic acid, reacts with a cyclam derivative and an aldehyde in water solution of an acid of a concentration within the range of from 10 to 40 % (weight), preferably from 18 to 36 % (weight), at the temperature in the range of from 40 °C to 80 °C for the period of time of at least 12 hours;

wherein the cyclam derivative is 1,4,8,11-tetraazacyclotetradecane and derivatives thereof and 1,4,8,11-tetraazabicyclo[6.6.2]hexadecane and derivatives thereof, preferably the cyclam derivative is selected from the group containing 1,4,8,11-tetraazacyclotetradecane, 1,4,8,11-tetraazabicyclo[6.6.2]hexadecane, 1,4,8-trimethyl-1,4,8,11-tetraazacyclotetradecane, 1,8-dimethyl-1,4,8,11-tetraazacyclotetradecane, 1,8-dibenzyl-1,4,8,11-tetraazacyclotetradecane, 1,4-dibenzyl-1,4,8,11-tetraazacyclotetradecane, 6,13-dimethyl-6,13-dinitro-1,4,8,11-tetraazacyclotetradecane;

the aldehyde is selected from the group containing acetaldehyde, formaldehyde and para-formaldehyde, and the acid is preferably HCl and/or CF_3COOH; and wherein the reaction may be preceded by the step of preparation of the intermediate product.

10. The method of preparation of the cyclam based compounds according to the claim 9, **characterized in that** the resulting product further undergoes a reduction reaction.

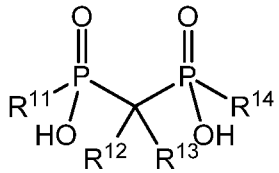
11. The method of preparation of the cyclam based compounds according to the claim 9, **characterized in that** the resulting product further undergoes an oxidation reaction.

12. The method of preparation of the cyclam based compounds according to the claim 9, **characterized in that** the resulting product further undergoes a reaction with an aldehyde; and eventually with an intermediate product of the general formula **(IV)**, or with a compound, selected from the group containing methylene-bis(phosphinic acid), phosphorous acid, alkylphosphinic acid or arylphosphinic acid; in water solution of an acid.

13. The method of preparation of the cyclam based compounds according to the claim 10, **characterized in that** the reduction step is followed by a step when the product of the reduction undergoes a reaction with $CSCl_2$ or $COCl_2$.

14. The method of preparation of the cyclam based compounds according to the claim 13, **characterized in that** the reduction step is followed by a step when the resulting product of the reduction undergoes a reaction with NaN_3.

15. An intermediate product of the general formula **(IV)** for the preparation of cyclam based compounds,



(IV)

wherein R^{11}, R^{12}, R^{13} and R^{14} are in the following combinations:

Intermediate	R^{11}	R^{12}	R^{13}	R^{14}

B	H	H	H	*p*-nitrobenzyl
C	H	H	H	$-CH_2N(benzyl)_2$
D	H	H	H	$-(CH_2)_2COOH$
E	H	$-(CH_2)_4COOH$	H	H
F	OH	$-(CH_2)_3NH$(4-dibenzylcyclooktynamidobutoxyl)	OH	OH

16. A pharmaceutical preparation, **characterized in that** it contains at least one cyclam based compound according to any one of the claims 1 to 5 and/or at least one conjugate according to the claim 6 and/or at least one coordination compound according to the claim 7 and/or at least one targeting conjugate according to the claim 8, and a pharmaceutically acceptable substance.

17. The cyclam based compound according to any one of the claims 1 to 5 and/or at least one conjugate according to claim 6 and/or at least one coordination compound according to the claim 7 and/or at least one targeting conjugate according to the claim 8 and/or the pharmaceutical preparation according to the claim 16, for use as a medicament, preferably in the treatment of tumor diseases, inflammations, and/or atherosclerosis.

18. The cyclam based compound according to any one of the claims 1 to 5 and/or at least one conjugate according to claim 6 and/or at least one coordination compound according to the claim 7 and/or at least one targeting conjugate according to the claim 8 and/or the pharmaceutical preparation according to the claim 16, for use as a contrast agent in medical diagnostics, preferably in the diagnostics of tumor diseases, inflammations, and/or atherosclerosis.

19. Use of cyclam based compounds according to any one of the claims 1 to 5 and/or at least one conjugate according to claim 6 and/or at least one coordination compound according to the claim 7 and/or at least one targeting conjugate according to the claim 8 and/or the pharmaceutical preparation according to the claim 16, in radiochemistry as markers or precursors of markers when labelling with the use of radioisotopes of copper, lutetium, bismuth and yttrium.

20. Use of cyclam based compounds according to any one of the claims 1 to 5 and/or at least one conjugate according to claim 6 and/or at least one coordination compound according to the claim 7 and/or at least one targeting conjugate according to the claim 8, for the complexation and/or purification of copper radioisotopes.

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/050043

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07F9/30 C07F9/38 A61K49/06 A61B5/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07F A61K A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	TOMÁS DAVID ET AL: "Cyclam Derivatives with a Bis(phosphinate) or a Phosphinato-Phosphonate Pendant Arm: Ligands for Fast and Efficient Copper(II) Complexation for Nuclear Medical Applications", INORGANIC CHEMISTRY, vol. 54, no. 24, 21 December 2015 (2015-12-21), pages 11751-11766, XP055335693, EASTON, US ISSN: 0020-1669, DOI: 10.1021/acs.inorgchem.5b01791 the whole document ----- -/--	1-20

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2017	26/01/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Johnson, Claire

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/050043

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/150302 A1 (UNIV MUENCHEN TECH [DE]; NOTNI JOHANNES [DE]; WESTER HANS-JUERGEN [DE]) 8 November 2012 (2012-11-08) claims 1,3,7,13 -----	1-20
A	MONIKA PAÚROVÁ ET AL: "Bifunctional Cyclam-Based Ligands with Phosphorus Acid Pendant Moieties for Radiocopper Separation: Thermodynamic and Kinetic Studies", CHEMISTRY - A EUROPEAN JOURNAL., vol. 21, no. 12, 3 February 2015 (2015-02-03), pages 4671-4687, XP055335710, WEINHEIM, DE ISSN: 0947-6539, DOI: 10.1002/chem.201405777 the whole document -----	1-20

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2016/050043

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012150302 A1	08-11-2012	NONE	

专利名称(译)	基于环己烷的化合物，它们的共轭物，共同化合物，含有它们的药物组合物，制备方法和用途		
公开(公告)号	EP3377504A1	公开(公告)日	2018-09-26
申请号	EP2016815699	申请日	2016-11-18
申请(专利权)人(译)	UNIVERZITA卡尔洛娃		
当前申请(专利权)人(译)	UNIVERZITA卡尔洛娃		
[标]发明人	DAVID TOMAS HERMANN PETR KUBICEK VOJTECH		
发明人	DAVID, TOMAS HERMANN, PETR KUBICEK, VOJTECH		
IPC分类号	C07F9/30 C07F9/38 A61K49/06 A61B5/00		
CPC分类号	A61K49/0002 A61K49/0021 A61K49/0041 A61K49/0043 A61K49/0052 A61K51/0402 A61K51/0453 A61K51/0459 A61K51/0482 A61K51/0489 A61K51/0497 A61K51/065 A61K51/08 A61K51/088 A61K51/1027 A61K51/1093 A61P29/00 C07F9/6524 C07F9/65583 C07F9/6561 C07F9/94		
优先权	2015825 2015-11-20 CZ		
外部链接	Espacenet		

摘要(译)

基于Cyclam的化合物，它们的共轭物，配位化合物，含有它们的药物组合物，其制备方法和用途本发明涉及通式（I）的环胞基化合物，这些化合物与缀合基团的缀合物，它们的配位化合物靶向缀合物，制备环连花青基化合物的方法，制备基于环胞基化合物的中间产物，含有它们的药物制剂及其用途。