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Cationic radionuclides and ligands for targeted therapeutic radiopharmaceuticals

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This review considers the already used and potential α- and β-emitting cationic radionuclides for targeted radionuclide therapy. Recent results of laboratory, preclinical and clinical applications of these radionuclides are discussed. As opposed to β-emitters, which are already used in nuclear medicine, α-emitters involved in targeted radiopharmaceuticals were subjected to clinical trials only recently and were found to be therapeutically effective. The review summarizes recent trends in the development of ligands as components of radiopharmaceuticals addressing specific features of short-lived cationic radionuclides applied in medicine. Despite a steadily growing number of chelating ligands, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and diethylenetriaminepentaacetic acid (DTPA) remain the most widely used agents in nuclear medicine. The drawbacks of these compounds restrict the application of radionuclides in medicine. Variations in the macrocycle size, the introduction and modification of substituents can significantly improve the chelating ability of ligands, enhance stability of radionuclide complexes with these ligands and eliminate the influence of ligands on the affinity of biological targeting vectors.
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The following designations and abbreviations are used:

AEM— alkaline-earth metals;

AMBA — peptide (bombesin analogue) – DOTA conjugate specific to GRP receptors;

BFC — bifunctional chelator;

Bq — becquerel (SI derived unit of radioactivity);

CHX-DTPA — 2-{bis[(carboxymethyl)amino]ethyl}-cyclohexane-1,2-diamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetic acid;

Ci — curie (non-SI unit of radioactivity, $1\,Ci = 3.7 \times 10^{10}$ Bq);

CT — computed tomography;

DEPA — {7-[2-(bis(carboxymethyl)amino)ethyl]-4,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl}acetic acid;

DOTA — 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid;

DOTMP — 1,4,7,10-tetraazacyclododecane-,4,7,10-tetramethylene phosphonic acid;

DTPA — diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetic acid;

EC — electron capture;

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EDTMP — ethylenediamine-*N*,*N*,*N*′,N′-tetramethylene phosphonic acid;

HEHA — 1,4,7,10,13,16-hexaazacyclohexadecane-1,4,7,10,13,16-hexaacetic acid;

ID/g — injected dose per gram of organ;

MAb — monoclonal antibody;

NETA — {4-[2-(bis(carboxymethyl)amino)ethyl]-7-carboxymethyl[1,4,7]triazonon-1-yl}acetic acid;

NOTA — 1,4,7-triazacyclononane-1,4,7-triacetic acid;

PCTA — 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid;

PEPA — 1,4,7,10,13-pentaazacyclopentadecane-1,4,7,10,13-pentaacetic acid;

PET — positron emission tomography;

PSMA — prostate-specific membrane antigen;

REE — rare-earth elements;

RP — radiopharmaceutical (in the context of this review, a targeting molecule labelled with a therapeutic radionuclide, the main active substance involved in the radiopharmaceutical);

rt — room temperature;

SPECT — single-photon emission computed tomography;

$T_{1/2}$ — half-life;

TCMC — 1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane;

TETA — 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid.

1. Introduction

Photon radiation produced during different types of radioactive decay allows the visualization of damaged tissues and the detection of metabolic disturbances. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are currently routine methods in medical diagnosis. Cancer therapy involves the particle radiation treatment (α- and β-particles, conversion and Auger electrons). As opposed to radiation therapy, which uses the ionizing effect of γ-radiation, targeted radionuclide therapy is based on the targeted delivery of radionuclides at a cellular level, which should provide a greater clinical response with less side damage of surrounding normal tissues. The DNA damage is a sufficient condition for its death. However, γ-radiation often induces DNA single-strand breaks, which are easily repaired because of complementarity. Particle emission characterized by high linear energy transfer can cause non-repairable DNA double-strand breaks and, consequently, irreversible cell death.

Currently, radionuclides of metals (^{64}Cu, ^{67}Cu, ^{88}Y, ^{90}Y, ^{89}Zr, ^{212}Pb, ^{177}Lu, ^{212}Bi, ^{213}Bi, ^{225}Ac, *etc.*) are extensively studied in nuclear medicine in order to use them for diagnosis and therapy of processes with different pharmacokinetics. Different types of radiation from the same radionuclide can be utilized in several nuclear medicine techniques. For example, β-radiation generated by ^{177}Lu is employed in cancer therapy, while its γ-radiation is applied in tumour imaging with SPECT. Besides, isotopes of the same element can be used for different medical purposes. For instance, the ^{64}Cu isotope is a radionuclide for PET, whereas the ^{67}Cu isotope is suitable for therapeutic applications.

Both molecular imaging and cancer therapy are based on the targeted delivery of a radionuclide to the damaged tissue, which can be achieved by using radionuclide-conjugated biological targeting vectors, such as antibodies, peptides, modular nanotransporters, *etc.*, having affinity to these cells. Radioactive isotopes of fluorine, carbon, bromine, iodine, astatine, *etc.* are incorporated into biological vectors by organic synthesis methods, *e.g.*, by the replacement of a hydroxy group with a fluoride anion or iodination of the amino acid tyrosine involved in a peptide. In order to use agents containing the ^{11}C isotope, radioactive carbon-labelled compounds chemically identical to a biological molecule are prepared. In all these cases, radionuclides are covalently bound to biological molecules.

Radionuclides being metal cations cannot be directly incorporated into a vector molecule. This is achieved by introducing a bifunctional chelator (BFC) into the targeting molecule. This chelator can form a stable complex with a radionuclide and is capable of being covalently bonded to a biological targeting vector. First, the use of BFCs extends the potential of nuclear medicine due to a significant increase in the range of radionuclides with appropriate nuclear-physical characteristics and can be introduced into radiopharmaceuticals (RPs). Second, a BFC–biomolecule conjugate can be synthesized in advance and its binding to a radionuclide, in order to incorporate biogenic elements, can be accomplished under easier conditions compared to organic synthesis. This allows the preparation of labelled complex biological compounds, such as monoclonal antibodies (MAbs), their fragments and peptides, which are impossible to prepare using synthetic methods and which can undergo degradation under synthesis conditions.

Special methods were developed for the preparation of BFC–biomolecule conjugates using appropriate functional groups in BFC. To retain affinity of the biomolecule after its modification by the introduction of a chelating agent, the latter is attached to a vector molecule not directly but *via* a linker, which may have a significant impact on the biodistribution and affinity.[1–3] Therefore, the most universal structure of the targeting molecule incorporated in RPs is composed of the following four functional moieties: a radionuclide, a BFC, a linker and a biomolecule (Fig. 1). The influence of the structure and nature of both the linker and the biomolecule on the efficacy of RPs in relation to the prospects of the use of therapeutic radionuclides is beyond the scope of this review.

The formation of a radionuclide–BFC complex depends on the individual characteristics of cations of different chemical nature, such as the coordination properties, the oxidation state and Pearson hardness, and on the BFC structure (the size, the presence and mutual arrangement of electron-donating heteroatoms and moieties involved in the coordination of metal ions).

According to the Web of Science, more than ten thousand studies on targeted radionuclide therapy, including several reviews,[4–9] in particular reviews on the application of individual radionuclides, reviews concerning appropriate chelators and those addressing the comparison of therapeutic effects of α- and β-radiation, were published in the last five years. This dynamically developing interdisciplinary field of chemistry requires the regularly updated systematization and integration of data. Here we endeavour to survey available data from the radiochemical point of view. This review focuses on studies of radionuclide–BFC complexes. We describe the main promising cations of thera-

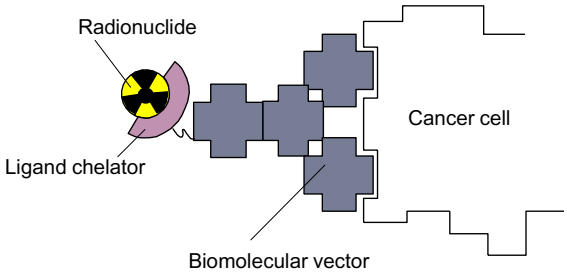


Figure 1. Schematic representation of a targeting molecule involved in a radiopharmaceutical.

peutic radionuclides (α- and β-emitters) and consider known ligands for their binding.

2. Cationic radionuclides for medical applications

Figure 2 shows a correlation between the type and energy of particles and their ranges in water.[10, 11] These characteristics are similar to those in biological tissues. β-Particles have a range of 100 – 1000 cell sizes, most energy being scattered at the end of the trajectory, which may cause damage not only to cancer cells but also to surrounding normal tissues, particularly in the case of micrometastases, freely circulating single cancer cells and residual tumours after surgery. α-Radiation is characterized by high linear energy transfer corresponding to a short range in tissue (5 – 10 cell sizes), resulting in that ionizing radiation is highly localized and, when entering the nucleus of the cell, induces multiple DNA double-strand breaks. Besides, noteworthy is the therapeutic effect of recoiling daughter nuclei arising from α-decay. These nuclei also have high linear energy transfer and a short range due to a large mass (see Fig. 2), thereby

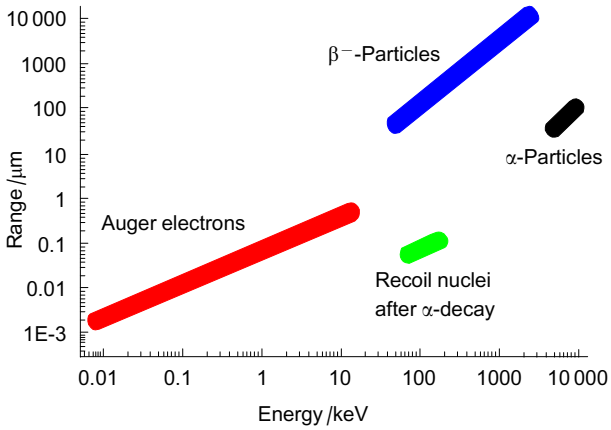


Figure 2. Correlation between the energy of different types of particles and their ranges in water.[10, 11]

enhancing a local toxic effect of α-radiation. On the other hand, the ranges of Auger electrons, due to their low energy, are from several nanometres to a micrometre, which is smaller than the cell size.[10] An Auger electron cascade can induce cluster DNA damage at the molecular level provided that an Auger emitter is delivered directly to the cell nucleus. Table 1 summarizes characteristics of selected therapeutic cationic radionuclides. Most RPs are diagnostic agents based on ^{99m}Tc, ^{67}Ga, ^{111}In, ^{123}I, ^{201}Tl (agents for SPECT), ^{18}F, ^{11}C, ^{13}N, ^{68}Ga, ^{82}Rb (agents for PET). A limited number of β-particle emitters (^{32}P, ^{89}Sr, ^{90}Y, ^{131}I, ^{153}Sm, ^{177}Lu) are utilized in therapeutic agents (see Table 1). A number of agents with α- and β-emitting radionuclides (^{90}Y, ^{177}Lu, ^{211}At, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{225}Ac, see Table 1) are currently at different stages of laboratory, preclinical and clinical trials. The only registered α-emit-

Table 1. Therapeutic cationic radionuclides and their characteristics.

Radionuclide	Half-life	Type of radiation produced from decay ($E_{\alpha,\beta max}$)	Range in tissue (p > 10%)	E_γ/keV	Ref.
^{90}Y	2.7 days	β⁻ (2280 keV)	β⁻: 10 – 12 mm	–	12
^{149}Tb	4.1 h	17% α (3967 keV),	α: 0.028 mm	165	13
		7% β⁺ (2451 keV),		352	
		76% electron capture (EC)		389	
				652	
				817	
				853	
^{153}Sm	46.3 h	β⁻ (808 keV)	β⁻: 0.3, 0.6 mm	103	14, 15
^{161}Tb	6.9 days	β⁻ (593 keV),	Auger:	46	16
		Conversion and Auger electrons	5×10^{-4} mm	49	
		(0 – 40 keV)	3×10^{-2} mm	75	
^{177}Lu	6.7 days	β⁻ (498 keV)	β⁻: 2 mm	208	12
^{212}Pb	10.6 h	β⁻ (574 keV)	–	239	17
^{213}Bi	0.75 h	2% α (5869 keV)	α: 50 – 100 μm	440	12, 18
		98% β⁻ (1427 keV)			
^{225}Ac	9.9 days	α (5935 keV)	α: 50 – 100 μm	218 (Fr-221)	12, 19
				440 (Bi-213)	
^{223}Ra	11.4 days	α (5716 keV)	α: 40 – 80 μm	269	12

ter-based radiopharmaceutical is $^{223}RaCl_2$ (Xofigo, Bayer), which is applied in the palliative treatment of bone metastases.

The efficiency of using the targeted drug is directly related to the specific radioactivity of the resulting molecule. Thus, an increase in the percentage of labelled molecules in RP reduces the competition for the binding to cancer cell receptors between the RP and cold non-radioactive molecules. This is responsible for the efficacy of radionuclide therapy. To increase the specific radioactivity, the synthesis of RP should be performed in the absence of impurity cations, including stable isotopes of the same element as therapeutic radionuclide (so-called carriers). The latter, being a chemically inseparable impurity, may significantly decrease the radiochemical yield of the labelling reaction, thereby decreasing the specific radioactivity. Hence, the choice of a radionuclide for nuclear medicine depends on the possibility of producing a carrier-free radioisotope.

The already used and potential radionuclides for medical applications include numerous representatives of rare-earth elements (REEs). Radionuclides of rare-earth elements have different half-lives and are characterized by different types and energy of radiation, while exhibiting similar chemical behaviour, including coordination properties. The Ac^{3+} cation is a close chemical analogue of La^{3+} and, correspondingly, exhibits chemical properties similar to those of REEs.[20] The similarity of chemical properties complicates the isolation of radionuclides of REEs in pure form after their production; however, it has a predictive value. Thus, the stability constants and structures of REE complexes are only slightly different, *i.e.*, the characterization of the structure of one complex with one REE provides insight into the binding of other REEs. All REEs, except for Ce, Eu, Sm and Yb, are stable only in oxidation state +3 and are Pearson hard cations. According to the lanthanide contraction, the ionic radius of the cation decreases from 1.216 Å [for the coordination number (CN) 9 for La^{3+}] to 1.032 Å [CN 9 for Lu^{3+} (see Ref. 21)] and its hardness increases with increasing atomic number of the cation. In complexes, these cations generally exhibit CN 9; in some cases, heavy-group REEs can have CN 8.[22]

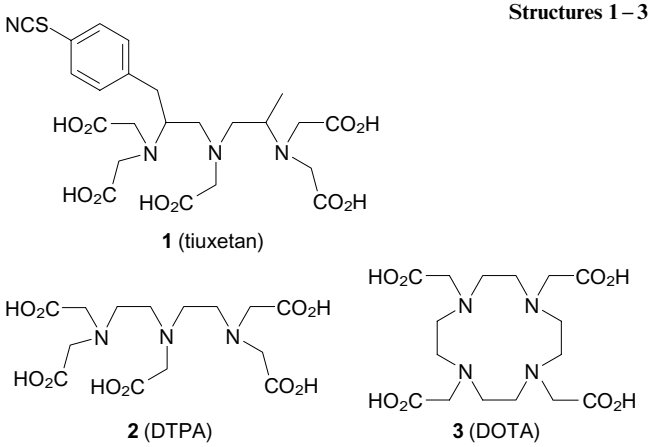
2.1. Yttrium-90

The ^{90}Y isotope can be prepared in carrier-free form using a $^{90}Sr/^{90}Y$ isotope generator. This isotope is a pure β-particle emitter that decays to the stable ^{90}Zr isotope. On the one hand, due to the absence of γ-radiation, there is no need to isolate the patient during radiotherapy. On the other hand, the absence of γ-radiation precludes the radionuclide molecular imaging. Radiopharmaceuticals containing positron-emitting yttrium isotopes (^{86}Y or ^{85m}Y) along with ^{90}Y can be employed in dosimetric studies and molecular imaging of the body. In the ionic form, Y^{3+} is accumulated in bones by replacing Ca^{2+}, which is applied in the palliative treatment of bone metastases.[23]

Due to a relatively long half-life of ^{90}Y (2.4 days), this isotope can be used with monoclonal antibodies, which can circulate in the bloodstream before the delivery to the target tissue for 1–2 days.[12] The drug Zevalin® (Biogen IDEC Pharmaceuticals), one of the first radioimmunotherapeutics for the treatment of non-Hodgkin's lymphoma, was developed based on a ^{90}Y-conjugated monoclonal antibody (2002).[12] Apart from the radionuclide, this drug contains Ibritumomab (a monoclonal antibody that was used to design the immunotherapeutic anticancer agent Rituxan (Roche Pharmaceuticals)) and the linker-chelator tiuxetan [**1**, a derivative of diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetic acid (DTPA, **2**)], which is covalently bound to the antibody and forms a stable complex with Y^{3+} through five carboxy groups and three amino groups.

The agents ^{90}Y-DOTATOC and ^{90}Y-DOTATATE based on 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA, **3**) conjugated with different synthetic analogues of somatostatin (octapeptides) for the treatment of patients with neuroendocrine tumours entered phase I and II clinical trials.[24–28] The application of these agents allows the targeted delivery of radionuclides to neuroendocrine cancer cells, resulting in full or partial remission, stabilization of the disease and 2–4-fold increased survival.

Structures 1–3



The drawback of ^{90}Y-based agents is high energy of β-radiation, which causes a deterioration of renal function[29,30] due to accumulation of yttrium-90 compounds in the kidneys. In the treatment with many peptide RPs, the absorbed dose to the kidneys can be decreased by the administration of the radiopharmaceutical in association with cold amino acids in order to block the corresponding peptide receptors in the kidneys.[31]

Since the ^{90}Y isotope does not emit penetrating γ-radiation, the imaging of the distribution of the administered ^{90}Y-labelled RP within the body cannot be performed by standard PET and SPECT techniques. The RP distribution in the body, which is used to evaluate the absorbed doses in all internal organs, including target tumour tissues, is individual for each patient. The bremsstrahlung SPECT imaging with the high-energy β-particle emitter ^{90}Y was

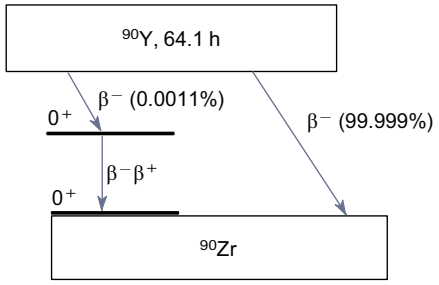


Figure 3. Decay scheme of ^{90}Y.[32]

applied in brachyherapy and peptide therapy. The use of PET/CT for this purpose was described in recent years.[25] Selwyn *et al.*[32] reported that the β^--particle emission that occurs in the ^{90}Y decay generates ^{90}Zr with a probability of 0.0011%, and the ^{90}Zr nucleus undergoes $0^+ - 0^+$ transition (Fig. 3) resulting in the emission of two 511 keV gammas in opposite directions, which can be detected by PET.[33]

2.2. Samarium-153

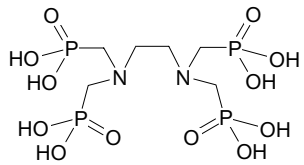
The ^{153}Sm isotope is characterized by β-radiation with maximum energy of 0.8 MeV, which corresponds to the mean range in tissue of *ca.* 0.6 mm.[15] The γ-emission with an energy of 103 keV in the decay scheme of ^{153}Sm allows the imaging of the drug distribution in the body and the calculation of dosimetric parameters.

Samarium-153 is prepared by thermal neutron irradiation of isotopically enriched samarium-152 oxide by the $^{152}Sm(n,\gamma)^{153}Sm$ reaction. The ^{153}Sm decay leads to the generation of stable ^{153}Eu. Samarium-153 with a specific activity of 222 GBq mg^{-1} is generated in a neutron flux of 1.2×10^{14} cm^{-2} s^{-1} for 155 h,[14] which corresponds to the conversion of only 1.5% of the starting Sm-152; consequently, the final preparation consists mainly (by 98.5%) of non-radioactive Sm-152, which significantly decreases its specific radioactivity.

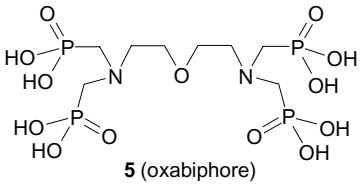
The low-molecular-weight ^{153}Sm complex with a phosphonate analogue of EDTA (ethylenediaminetetramethylene phosphonic acid, EDTMP, **4**), the drug Quadramet (Lantheus Medical Imaging), is used in the palliative treatment of bone metastases.[34] Since ^{153}Sm emits β-radiation with a short range in tissue (see Table 1), it can be used for cell killing in a local area. Hence, ^{153}Sm-labelled RPs are less toxic to normal tissues surrounding tumours compared to the high-energy β^--emitter ^{90}Y. The treatment of bone metastases is accompanied by radiation damage to bone marrow, which has a negative impact on the general state of the patient. Therefore, β-emitting ^{153}Sm, the energy of which is lower than that of the β-emitter ^{90}Y, is preferable for therapy. The presence of γ-radiation makes it possible to perform the treatment simultaneously with SPECT imaging, which allows the observation of the drug accumulation in tumours; in the case of repeated administration, it allows the assessment of the dynamics and outcome of therapy. Due to a short half-life, high doses of the agent can be used, which ensures a rapid clinical effect.

The drug ^{153}Sm-oxabiphore (**5**) was registered in Russia in 2000. The mechanism of action of this agent is similar to that of ^{153}Sm-EDTMP.[35] The radionuclide is delivered to tumours with high mineralization demands, and the drug, which does not bind to bone tissue, is rapidly excreted from the body by the kidneys.[34]

Structures 4, 5



4 (EDTMP)



5 (oxabiphore)

2.3. Terbium-149 and terbium-161

The ^{149}Tb isotope is characterized by a rather complex decay scheme (see Table 1, Fig. 4). The positron emission and electron capture generating ^{149}Gd occur with 83% probability, and α-decay (17%) produces ^{145}Eu. Daughter radionuclides are longer-lived compared to ^{149}Tb, which provides 33.3% radiation, while ^{149}Tb itself contributes 66.7% of the radiation dose.[36]

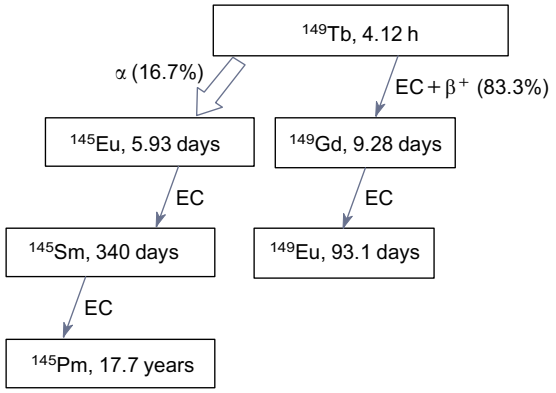
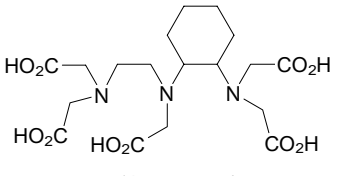


Figure 4. Decay scheme of ^{149}Tb.

The difficulties of producing ^{149}Tb limit its application. Thus, ^{149}Tb is generated by the irradiation of REE oxides with light and heavy ions, *e.g.*, $^{152}Gd(\alpha,7n)^{149}Dy \rightarrow {}^{149}Tb$; $^{144}Sm(^{9}Be,4n)^{149}Dy \rightarrow {}^{149}Tb$; $^{142}Nd(^{12}C,5n)^{149}Dy \rightarrow {}^{149}Tb$. Besides, ^{149}Tb can be prepared by the proton-induced spallation of tantalum foil targets, $^{180}Ta(p,spallation)^{149}Tb$. Terbium-149 produced in these reactions is purified from other REEs by chromatography. This procedure is rather complicated and involves several stages.[13] Since ^{149}Tb has a relatively short half-life (4 h), an insignificant loss of its radioactivity occurs during the purification from longer-lived daughter radionuclides and the synthesis of RPs.

Due to low α-emission probability (16.7%), the efficient use of ^{149}Tb requires high expression of tumour-specific antigens for ^{149}Tb-labelled antibodies in cancer cells, while surrounding normal tissues are not damaged due to low α-particle energy from ^{149}Tb.[37] The treatment of single leukemia cells freely circulating in the blood with the ^{149}Tb-labelled monoclonal antibody rituximab against leukemia cells conjugated with 2-{bis[carboxymethyl)amino]ethyl}cyclohexanediamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetic acid (CHX-DTPA, **6**) — ^{149}Tb-CHX-DTPA-Rituximab — resulted in 90% survival rate in mice.[36] The use of ^{149}Tb-DOTA with another biological vector (a folic acid derivative) produced an effective therapeutic response in

Structure 6



6 (CHX-DTPA)

mice with formed tumour mass. This treatment led to a twofold increase in the survival time of mice.[38]

Due to the presence of β^+-radiation in the decay scheme of ^{149}Tb, the latter can be used in PET imaging of RPs, which was successfully performed in xenografted mice.[39]

Terbium-161 can also be used for radiotherapeutic purposes. This isotope is similar in nuclear-physical and chemical properties to ^{177}Lu (see Table 1). However, as opposed to ^{177}Lu, ^{161}Tb emits, along with β-radiation, conversion and Auger electrons with 27% probability.[40] Terbium-161 is produced by irradiating a highly enriched ^{160}Gd target, resulting in the generation of ^{161}Gd, which is rapidly ($T_{1/2}$ = 3.7 min) β^--decays to ^{161}Tb. It is important that ^{160}Gd should be pure because an impurity of stable ^{159}Tb gives rise to long-lived inseparable ^{160}Tb ($T_{1/2}$ = 72.3 days). Besides, the accumulation of the daughter nuclide ^{161}Dy with very similar chemical properties in ^{161}Tb also decreases the specific radioactivity of the resulting RP.[40]

Conversion and Auger electrons can significantly increase the local therapeutic effect in the case of intercalation of RP into DNA.[41] A ^{161}Tb-labelled folic acid derivative which had no affinity directly to the cancer cell nucleus[16] exhibited higher therapeutic potential in *in vitro* (cell lines) and *in vivo* (xenografted mice) experiments compared to ^{177}Lu. The assessment of renal toxicity of ^{161}Tb and ^{177}Lu folates in mice revealed very similar side effects of both radionuclides.[42] This fact indicates that conversion and Auger electrons from ^{161}Tb exert an insignificant effect on nephrotoxicity. Besides, the therapeutic efficacy of the peptide agent ^{161}Tb-DOTATATE is comparable with that of ^{177}Lu-DOTATATE, which is already used as a radiopharmaceutical.[40]

Due to the presence of γ-radiation, ^{161}Tb can be employed in SPECT imaging of the radionuclide distribution in the body,[16] and, taking into account its low energy (see Table 1), it can be considered as a candidate for the detection of the accumulated labelled peptide in tumours during surgery.[43] This cannot be accomplished using higher-energy γ-emitters (*e.g.*, ^{111}In), which are characterized by high background values, thereby complicating the localization of small tumours with a special probe detector.

2.4. Lutetium-177

The ^{177}Lu isotope is a soft β-emitter (see Table 1) and, consequently, it has a short range in tissue, thereby providing local therapy. Hence, this isotope is a less toxic alternative to ^{90}Y, which makes it possible to reduce the absorbed dose to the kidneys and to treat a patient with repeated cycles.

The production of the ^{177}Lu isotope by the reaction ^{176}Lu(n,γ)^{177}Lu gives rise to chemically inseparable impurities of the starting stable ^{176}Lu isotope and long-lived ^{177m}Lu, which adversely affects the radiochemical purity of ^{177}Lu-labelled RPs. The formation of these inseparable impurities can be avoided using the reaction ^{176}Yb(n,γ)^{177}Yb followed by the decay of ^{177}Yb ($T_{1/2}$ = 1.9 h) to ^{177}Lu.[44] In this case, the separation of Lu^{3+} and Yb^{3+} is required.

Synthetic analogues of somatostatin (octapeptides) labelled with ^{177}Lu have been extensively used for a long time for the treatment of patients with neuroendocrine tumours.[45–47] Clinical trials[48] demonstrated that any response to the treatment with ^{177}Lu-DOTATATE (stabilization of the disease, partial or complete response) leads to an increase in the survival rate and improvement of quality of life, partial or complete response being observed in 29% treated patients. The drug Lutathera (developed by Advanced Accelerator Applications) containing the ^{177}Lu-DOTATATE complex has passed all phases of clinical trials and was approved in 2018 by the Food and Drug Administration (FDA).[4]

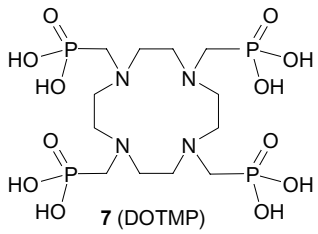
Interesting results were obtained upon radionuclide treatment of large metastatic malignancies in rats with pancreatic cancer xenografts using β-radiation with different energy in combination of the agents ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE.[49] The application of the high-energy emitter ^{90}Y results in the inhibition of tumour growth for large tumours, while the medium-energy emitter ^{177}Lu leads to at least a twofold increase in survival. The therapy of patients with relapse of tumours after the treatment with ^{90}Y-DOTATOC can also be successfully performed with ^{177}Lu-DOTATOC, which has a less adverse effect on the kidneys.[50]

Apart from ^{177}Lu-DOTATATE, ^{177}Lu-labelled bombesin-like peptides (^{177}Lu-AMBA, where AMBA is a DOTA – peptide conjugate specific to GRP receptors) were also subjected to clinical trials.[51] Bombesin-like peptide receptors are expressed in prostate, breast and pancreatic cancer cells, the pancreas rather than the liver or kidneys is under risk and it is a critical organ controlling the administered dose. Experiments in mice bearing xenografted prostate tumours showed that ^{177}Lu-AMBA causes a twofold inhibition of tumour growth due to the damage of its actively developing vessels.[52] Lim *et al.*[53] developed other ^{177}Lu-labelled bombesin analogues — antagonists, which are less accumulated in other organs expressing this receptor.

Apart from ^{153}Sm, ^{177}Lu-labelled phosphonate analogues of DOTA and EDTA are in clinical trials as agents for the palliative treatment of bone metastases. It was shown that ^{177}Lu-DOTMP (1,4,7,10-tetraazacyclododecane-1-4,7,10-tetramethylene phosphonic acid, **7**) and ^{177}Lu-EDTMP (ligand **4**)[54] are nearly equally effective regarding the distribution in the body, but the latter agent exhibits lower *in vitro* acid stability of complexes typical of acyclic ligands. Clinical trials of ^{177}Lu-EDTMP (phases I and II) showed that the therapeutic effect is already achieved at the administered dose of 1300 MBq and administration is possible up to 2600 MBq.[4,55] This drug and Quadramet (^{153}Sm-EDTMP, Lantheus Medical Imaging), when used in the same dose, are characterized by similar efficacy of the palliative treatment and similar side toxicity to bone marrow.[56,57] Therefore, ^{177}Lu is a longer-lived alternative to ^{153}Sm for the preparation of phosphonate RPs as agents for the palliative treatment of bone metastases.

In recent years, the ^{177}Lu-labelled inhibitor of the prostate-specific membrane antigen (PSMA) was clinically

Structure 7



7 (DOTMP)

studied as an agent for prostate cancer therapy.[26, 58] It was found that one-third of patients do not have a clinical response to the therapy with ^{177}Lu-PSMA617 [the PSMA – DOTA conjugate (**3**)], which is attributed primarily to nonuniformity of the distribution of PSMA receptors on membranes of cancer cells or to their absence.[58] The positron emitter ^{68}Ga, which is introduced into PSMA617 through the DOTA (**3**) ligand, can be applied for imaging of tissues with binding affinity for PSMA617 and, hence, for the evaluation of potential therapeutic efficacy of ^{177}Lu-PSMA617 and the absorbed doses to tumour and normal organs. The use of ^{77}Lu for the treatment of bone metastases of prostate cancer leads to a significant suppression of the bone marrow function due to a rather long range of β^--particles, which not only kill cancer cells in bone metastases but also penetrate bone marrow cells.[58]

For the relatively long-lived ^{177}Lu isotope, it is possible to use high-molecular-weight protein constructs, such as antibodies and proteins with longer clearance from the body. Therefore, in recent years, efforts were made to prolong the action of an administered single dose, which should lead to a higher therapeutic effect.[1, 2, 59] Labelled antibodies[59] or the agents DOTATATE[1] and PSMA617[2] modified with an albumin-binding fragment (Evans Blue EB) are applied for this purpose. First clinical trials[1, 2, 26] showed that this approach leads to a 3 – 8-fold increase in the accumulation of the radioactive emitter in the tumour; however, a significant increase (7 – 18 times) in the adsorbed dose to the bone marrow is observed as a side effect.

2.5. Actinium-225

Actinium-225 is an α-particle emitter. It decays *via* a cascade of six relatively short-lived daughter radionuclides, including ^{213}Bi, to long-lived ^{209}Bi ($T_{1/2} = 1.9 \times 10^{19}$ years) and generates a total of four α-particles with a cumulative energy of 28 MeV per ^{225}Ac decay (Fig. 5). The distribution in the body can be monitored using the γ-emitters ^{221}Fr (218 keV) and ^{213}Bi (440 keV).

The ^{225}Ac isotope is a daughter decay product of ^{229}Th ($T_{1/2} = 7.34 \times 10^3$ years), which is, in turn, the decay product of ^{233}U. An amount of ^{225}Ac produced from ^{229}Th (63 – 68 GBq × year^{-1}) is sufficient for preclinical and few clinical trials. However, it is necessary to increase the production of ^{225}Ac in order to realize the widespread clinical use. New ^{225}Ac production methods are being developed. For example, one method involves the irradiation of the ^{226}Ra isotope with neutrons, protons and photons, as well as the irradiation of natural ^{232}Th with high-energy protons.[5, 19, 60, 61] The production of ^{225}Ac by the irradiation of natural thorium targets with medium-energy protons is hampered by the presence of a chemically inseparable impurity of the longer-lived (compared to ^{225}Ac) ^{227}Ac isotope ($T_{1/2} = 21.8$ years), which accounts for 0.1 – 0.2% radioactivity at the end of irradiation. Hence, the clinical use of this actinium isotope is an open question. Jiang *et al.*[62] performed the *in vivo* biodistribution study of free Ac^{3+} (^{225}Ac + ^{227}Ac from a proton-irradiated thorium matrix) in mice. The distribution pattern and the absorbed dose are similar to those of $^{225}Ac^{3+}$ produced from ^{29}Th.

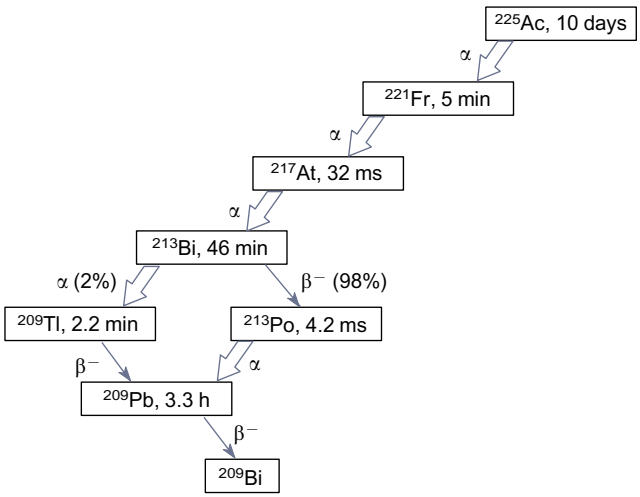


Figure 5. Decay scheme of ^{225}Ac.

Due to a relatively long half-life, ^{225}Ac can be used in bioconjugates with monoclonal antibodies, which have a long circulation time in the body. The labelled conjugate ^{225}Ac-DOTA-MAb is an *in vivo* generator ^{213}Bi. The prospects of its therapeutic application were demonstrated using different antibodies in leukemia, lymphoma, breast cancer and prostate cancer cell lines. It was shown that a similar effect for ^{225}Ac is achieved by the administration of a 100 – 1000 times lower dose of radioactivity compared to its daughter isotope, the relatively short-lived α-emitter ^{213}Bi.

Currently, ^{225}Ac is in clinical trials as an agent for the treatment of neuroendocrine tumours, prostate cancer and leukemia. About 250 patients have been treated or are being treated with ^{225}Ac-containing RPs.[5]

The radiopharmaceutical ^{225}Ac-lintuzumab (lintuzumab is a monoclonal antibody against leukemia cells) is in ongoing clinical trials since 2006.[26, 63, 64] In these studies, the RP was applied together with chemotherapy. The positive response in 28% patients is already observed after the first cycle of chemotherapy, while the chemotherapeutic agent cytarabine causes a response, on the average, only after the third cycle.

The actinium-labelled octreotide ^{225}Ac-DOTATOC, which proved to be effective in *in vitro* experiments,[65] was used in clinical conditions for the determination of a tolerable dose after the single (40 MBq) or systemic administration (25 MBq every four months, 18.5 MBq every two months).[66] Two cycles of therapy with this agent lead to a significant decrease in the amount of metastases due to a partial response to therapy.[5]

Promising results were obtained in recent studies of the application of the ^{225}Ac-labelled inhibitor PSMA in the treatment of metastatic prostate cancer.[67] Three to four administrations of ^{225}Ac-PSMA617 at doses of 6 – 10 kBq not only led to a decrease in the prostate-specific antigen level (PSA is a marker for prostate cancer) in the blood but also reduced diffuse metastatic bone marrow infiltration. Meanwhile, the complete absence of response was observed after two administrations of ^{177}Lu-labelled PSMA. Despite successful results in the treatment of prostate cancer, in the long term (the absence of remission during 1 – 2 years), the repeated use of ^{225}Ac-PSMA617 in this form is not always possible because this ligand has affinity to salivary glands, thereby impairing their secretion.[68] Apart from PSMA617, MAb J591 with longer pharmacokinetics[26] was proposed as

a delivery vector for ^{225}Ac. Earlier, this vector was used in studies with β-emitting ^{177}Lu for the treatment of prostate cancer.[59]

In the case of α-particle emitters, particularly ^{225}Ac as a α-particle cascade emitter, the release of cations of daughter radionuclides of ^{221}Fr and other α-emitters from complexes is of great importance. Thus, the nuclear recoil energy (E_{av} = 120 keV) resulting from α-particle emission leads to the release of radioactive daughter ^{221}Fr isotope from a chelator complex. However, this is not critical in the case of localization of ^{225}Ac in the tumour.[69] If daughter radionuclides are released into the bloodstream, the $^{213}Bi^{3+}$ cation is taken up by transferrin,[70] which is retained by the kidneys. Correspondingly, nephrotoxicity of ^{225}Ac is due to ^{213}Bi radiation. The use of additional chelating agents for *in vivo* uptake of the released radionuclide or the administration of the stable isotope of Bi^{3+} makes it possible to decrease the absorbed dose to the kidneys by 14% – 45%.[71]

2.6. Bismuth-213

Radiopharmaceuticals containing the α-emitting radionuclide ^{213}Bi are in ongoimg clinical trials. This radionuclide is a mixed β- (98%) and α-emitter (2%) (see Table 1). However, its decay products include the pure α-emitter ^{213}Po and the β-emitters ^{209}Tl and ^{209}Pb, resulting in its high therapeutic efficacy, which was demonstrated in the treatment of glioma (including glioblastoma) of the brains.[18, 72] Besides, despite a short half-life of ^{213}Bi (see Table 1), its application with MAbs is in clinical trials for the treatment of leukemia [73, 74] melanoma [75, 76] and bladder cancer.[77] Due to γ-radiation, ^{213}Bi-labelled RPs are suitable for SPECT imaging.

In solution, bismuth has oxidation state +3; the ionic radius of Bi with CN 8 is 1.17 Å.[21] The Bi^{3+} ion is characterized by high affinity to donor oxygen and nitrogen atoms and high (compared to trivalent cations of other metals) stability constants of its complexes with polyaminopolycarboxylates [78] and of its hydrolysis species (hydroxy complexes are already formed at pH 1).[79] Besides, the Bi^{3+} ions forms stable halides due to which ^{213}Bi can be eluted from the ^{225}Ac/^{213}Bi generator based on AG MP-50 cation exchange resin with a 0.1 M NaI solution in HCl. The availability of this isotope is related to the ^{225}Ac production. Due to a short half-life, the elution of ^{213}Bi from the generator can be performed every 4 – 5 h. The effect of radiolysis should be taken into account when using a ^{225}Ac/^{213}Bi generator for the construction of a generator system. To decrease the effect of radiolysis, the parent radionuclide is loaded onto a chromatographic column in such a way that the radioactivity is uniformly distributed along 2/3 of the column (in the case of AG MP-50).[19] Another approach is based on the elution of the parent radionuclide before or after the daughter radionuclide and the storage of the generator solution for further isolation.[80] In some cases, the tandem separation scheme is applied, particularly in the case of ^{213}Bi elution after ^{225}Ac elution. Thus, to perform the additional purification, the eluate containing ^{213}Bi is passed through the second column. However, the separation may lead to considerable loss of radioactivity.

First clinical trials of the peptide agent ^{213}Bi-DOTA-SP (SP, Substance P, peptide specific to brain cancer tumours) for the treatment of glioma showed that the radionuclide distribution in the entire volume is possible in the case of relatively small tumours (12 – 17 cm^3), whereas larger tumours are mainly necrotic in a small volume.[72] Necrotic tissues are easily separated during surgery, and even the visually distinguishable demarcation between the tumour and normal tissues is observed. The lower the dose of ^{213}Bi, the more rapid the tumour recurrence. Thus, the tumour progression was not observed only within one month after the injection of a dose lower than 1.07 GBq, whereas there was no evidence of tumour progression in the following 24 months after the injection of 7.36 GBq. The health status of all patients was improved after the therapy. A further escalation in the dose to 11 GBq (Ref. 18) led to an increase in survival in 40% patients with glioblastoma (the most aggressive and malignant brain tumour) from 15 to 18 months (studies are underway).

The advantage of α-radiation in certain cases was demonstrated in relation to the therapy of patients with neuroendocrine tumours resistant to therapy with ^{90}Y and ^{177}Lu.[81] The peptide agent ^{213}Bi-DOTATOC (a total of 20.6 GBq with 4 – 5 injections) proved to be effective for all patients (8 patients) with neuroendocrine tumours with hepatic metastases, for which the absence of disease progression (7 patients) and complete remission (1 patient) over 17 – 31 months were observed. In this case, RP was injected intra-arterially (*via* a catheter in the hepatic artery) rather than intravenously, which facilitates better localization in the liver. The drug accumulation was monitored by SPECT using the γ-emitter ^{213}Bi (440 keV) and the final image was compared with the PET/CT image obtained using ^{68}Ga-DOTATOC.

Like ^{225}Ac-PSMA, the ^{213}Bi-PSMA complex was found to be promising in the treatment of tumours resistant to the β-emitter ^{177}Lu, which was demonstrated by first clinical trials.[82]

The treatment of leukemia with the β-emitters ^{90}Y and ^{131}I conjugated with antibodies against leukemia cells proved to be effective; however, this treatment is highly toxic to bone marrow because β-emitters are long-range particles.[74, 83] In this case, the use of α-particle emitters, in particular ^{213}Bi-CHX-DTPA-lintuzumab (CHX-DTPA, ligand **6**), is more reasonable.[74] The highest efficacy and lower toxicity were observed in the combination chemotherapy with cytarabine, which resulted in a decrease in the tumour size, followed by the administration of RP. At a dose of $\geqslant$37 MBq kg^{-1}, a clinical response was observed in 6 of 18 patients with primary myeloid leukemia (ML), whereas the therapeutic effect was absent in 7 previously treated patients with resistant ML.

Agents for the treatment of melanoma are ^{213}Bi-DTPA-MAb9.2.27 conjugates [anti-melanoma monoclonal antibody 9.2.27 conjugated with DTPA (**2**)]. In the cases of response (stabilization of the disease or partial response), the median survival increased from 266 to 612 days, and almost complete recovery was observed in one of 38 patients. Allen *et al.*[75] suggested that the therapeutic effect of α-radiation on large solid tumours, despite the short range of these particles, is achieved due to the closure of capillaries in the tumour, resulting in the regression of the tumour caused by oxygen and nutrient starvation.[84]

The targeted α-immunotherapy of bladder cancer with ^{213}Bi-labelled MAb proved to be effective. In this case, like in the treatment of glioma, RPs are injected directly into the area of the tumour (bladder) taking into account a short half-life of ^{213}Bi and prolonged pharmacokinetics of MAb.

Complete recovery and the absence of recurrence over 3, 30 and 44 months was observed in three of 12 patients, which significantly improved quality of life of the patients subjected to radical cystectomy.[77]

2.7. Lead-212

The ^{212}Pb isotope emits β-particles and Auger electrons, as well as conversion electrons; however, the therapeutic effect of this isotope is associated with α-radiation of its daughter radionuclide ^{212}Bi (Fig. 6). Hence, ^{212}Pb-based RPs act as *in vivo* generators of ^{212}Bi. Besides, the short half-life of ^{212}Bi ($T_{1/2}$ = 60.6 min) hampers the use of monoclonal antibodies as biological vectors, while this problem can be avoided using ^{212}Pb ($T_{1/2}$ = 10.6 h). The presence of high-energy (probability 99%) γ-emission from ^{208}Tl in the decay chain will require special conditions for housing of patients and will provide high doses exposure of medical staff. Apparently, ^{212}Pb can be produced from the ^{224}Ra/^{212}Pb isotope

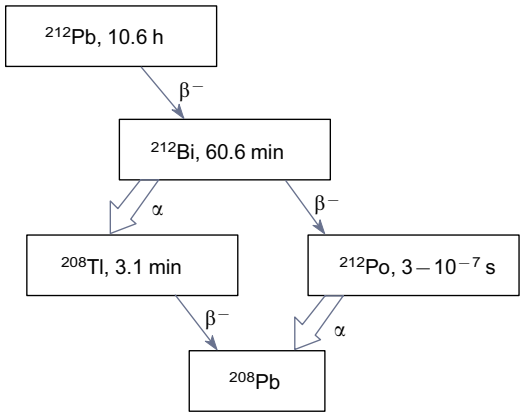


Figure 6. Decay scheme of ^{212}Pb.

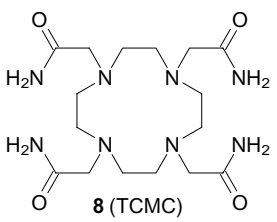
generator (*e.g.*, Areva Med).[85, 86]

The typical oxidation state of lead is +2, and its ionic radius for CN 6–12 is 1.19–1.49 Å.[21] The Pb^{2+} cation is a borderline soft acid according to Pearson's theory.

The therapeutic efficacy of ^{212}Pb was first demonstrated in melanoma xenografts in mice.[87] An increase in survival and suppression of tumour growth were observed in 45% of mice after the injection of 7.4 MBq.

Clinical trials[26] of the ^{212}Pb-TCMC-trastuzumab conjugate [trastuzumab is a monoclonal antibody; 1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane (TCMC, **8**) serves as BFC] as an agent for the therapy of abdominal cancer (16 patients) demonstrated that the administration of 7.4–21.1 MBq m^{-2} leads to disease stabilization. Due to a short half-life of the ^{212}Pb isotope, the general toxicity of RPs to the entire organ significantly decreases, which makes it possible to administer higher doses to achieve a high therapeutic effect, as demonstrated by a comparison with ^{90}Y-labelled RP.[88–90]

Structure 8



8 (TCMC)

Studies aimed at the improvement of procedures for the production of ^{212}Pb-labelled molecules are underway. For example, it was proposed to use the ^{224}Ra/^{212}Pb generator based on cation exchange resin (AlphaMed).[91] This procedure involves the repeated evaporation and repeated dissolution of the eluate from this generator in acids to transfer the cation from a strongly acidic medium to the acetate buffer. This, along with the quality control, is time-consuming. A procedure was proposed for the extraction of ^{212}Pb directly from a solution of ^{224}Ra, which occurs in secular equilibrium with its daughter radionuclides, with a 0.1 M HCl–0.5 M NH_4OAc mixture using an antibody conjugate.[92] The conjugate can capture only the ^{212}Pb isotope and subsequent radionuclides in the decay chain of ^{224}Ra. However, additional purification from ^{224}Ra is required. This is accomplished by gel filtration chromatography.

Another approach to the optimization of the synthesis of ^{212}Pb in a form suitable for the preparation of RPs involves the preconcentration of ^{212}Pb from the starting solution in 2 M HCl on a chromatographic column (Pb-resin, Eichrom Technologies) using elution with a 0.5 M NaOAc solution (pH 6).[93] The ^{212}Pb isotope thus generated was introduced into labelled peptides specific for neuroendocrine tumours and melanoma.

2.8. Radium-223

As mentioned above, the ^{223}Ra isotope is the only α-emitter, which is present in the registered RP (Xofigo, Bayer) and is applied in the palliative treatment of bone metastases in prostate cancer. This drug is an aqueous solution of radium-223 chloride. Radium belongs to alkaline-earth metals (AEMs) and is similar to calcium, which provides its targeted accumulation in highly mineralized regions of the skeleton affected with metastatic tumour growth. The half-life of 11 days makes it possible to prolong the palliative care provided by five α-particle emitters (Fig. 7). On the other hand, due to high Pearson hardness of AEMs, their binding by chelating agents is a challenge that remains to be

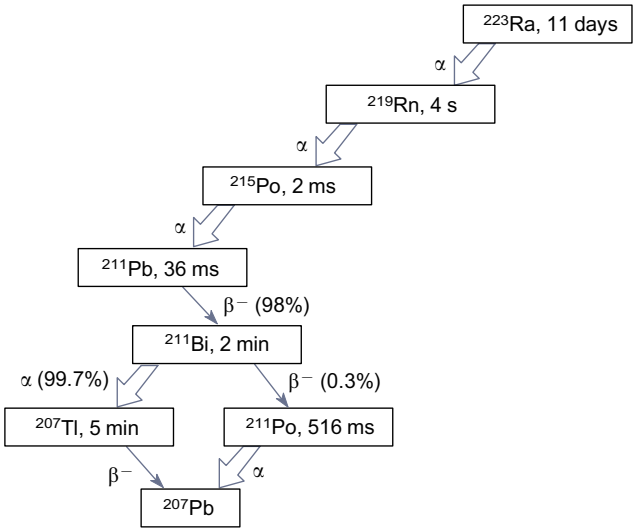


Figure 7. Decay scheme of ^{223}Ra.

solved, and the application of ^{223}Ra is limited to the treatment of bone metastases.[94,95] The incorporation of a radionuclide in carriers, *e.g.*, nanozeolites, functionalized with a biological vector (Substance P), which retain affinity to particular cancer cells, is a possible approach to the production of a ^{223}Ra-labelled targeting agent.[96] The use of $^{223}RaCl_2$ in combination with chemotherapy and immunotherapeutic agents is currently extensively studied in ongoing clinical trials.[26]

3. Complexes with chelators for radiopharmaceuticals

Due to ability to form highly stable complexes with ions of radionuclides, macrocyclic and acyclic chelate derivatives are extensively used as components of diagnostic and therapeutic anticancer agents — radiopharmaceuticals.

When considering different chelators, one should bear in mind that therapeutic cationic radionuclides have not only different oxidation states and ionic radii (Table 2) but also different Pearson hardness. To compare the hardness of cations, it is convenient to use the bond ionicity $I_A = E_A/C_A$,[97] where E_A is an electrostatic component of the bond formation in the complex in aqueous solution and C_A is a covalent component. For comparison: the I_A values for Hg^{2+} (a representative of soft cations) and Th^{4+} (a representative of hard cations) are 1.63 and 10.94, respectively. As can be seen from these values (see Table 2), REE cations are the hardest ones, whereas Bi^{3+} and Pb^{2+} cations occupy an intermediate place, *i.e.*, are borderline cations.

Table 2. Radii (CN 6)[21] and hardness parameters[97] of cations.

Cation	Bi^{3+}	Pb^{2+}	Lu^{3+}	La^{3+}	Y^{3+}	Ra^{2+}
R/nm	0.103	0.095	0.0861	0.1032	0.090	0.148 (CN 8)
I_A	6.39	6.69	10.07	10.3	10.64	12.7 (Ba^{2+})

The most important requirement for complexes of cationic radionuclides with chelators are considered below.

Thermodynamic stability. A radionuclide as a component of RP is administered to the body at a concentration of 10^{-9}–10^{-6} M, which may lead to dissociation of the cation–chelator (M–L) complex. High thermodynamic stability enables the final complex to remain intact. The complexation with acyclic ligands is accompanied by the arrangement of donor atoms around the metal cation, resulting in a decrease in the entropy of the system. In the case of macrocyclic ligands, the macrocyclic cavity is preorganized for complexation, *i.e.*, the formation of complexes with macrocyclic ligands is thermodynamically favourable (so-called macrocyclic effect).[6,98]

Table 3 gives the logarithms of stability constants for the complexes of the chelators DTPA (**2**) and DOTA (**3**), which are most commonly used in RPs, with cations of important therapeutic radionuclides. As can be seen in Table 3, the stability constants of all these complexes are rather high, but the $\log K_{ML}$ values for cyclic ligand **3** are larger than the corresponding values for DTPA (**2**).

Kinetic stability. A biological medium contains numerous cations of microelements (Ca^{2+}, Cu^{2+}, Zn^{2+} and Fe^{3+}) competing for the chelator, ligand ions to bind radionuclide cations (hydroxide and phosphate ions), serum proteins and enzymes at concentrations several orders of magnitude higher than those of RPs. For example, the concentration of Ca^{2+} ions in the blood is 5×10^{-3} mol litre^{-1}. Hence, the used radionuclide–BFC complex should be stable in the presence of competing cations and ligands, *i.e.*, it should be kinetically stable.

Table 3. Logarithmic stability constants of selected complexes with cations under consideration.[6]

Cation	log$K$(M–DOTA)	log$K$(M–DTPA)	Ref.
Y^{3+}	24.3–24.9	21.2–22.5	6
Tb^{3+}	26.2	22.7	22
Sm^{3+}	26.1	22.3	22
Lu^{3+}	25.5, 23.5, 21.6	22.4	22
Ac^{3+}	–	–	
Bi^{3+}	30.3	35.2	99, 100
Pb^{2+}	22.7	–	98

One of parameters characterizing kinetic stability of the complexes is the rate of dissociation in an acidic medium because antibodies are transferred to an acidic medium during metabolism. Besides, the stability in an acidic medium is a convenient tool for the preliminary assessment of stability of complexes. The stability of cation–chelator complexes in the serum is initially examined *in vitro* and *in vivo* in healthy laboratory animals in order to assess the possibility of releasing cations during metabolism. The conjugation to biological vectors can affect the complexation ability of the ligand. Hence, conjugates are tested in several steps: in cell lines *in vitro* and in laboratory animals bearing xenografted tumours *in vivo*. In all *in vivo* experiments, the accumulation of radionuclides in filtration organs (kidneys, liver), the effect on bone marrow and the rates of uptake in the tumour and release from the body are evaluated. These parameters characterize kinetic stability of the complex *in vivo*.

Conditions for the synthesis of complexes. Radionuclides applied in nuclear medicine are characterized by a relatively short half-life (from several minutes to several days, see Table 1). The loss of radioactivity during the synthesis of RP should be as small as possible, which requires the rapid preparation of radionuclides (elution from the generator, purification from daughter radionuclides) and the rapid complexation with a ligand (conjugate). Besides, the conditions of administration to the body (pH of the medium, the temperature and the volume of the administered agent) should be taken into account. The synthesis at elevated temperature can lead to the destruction of biological vectors. Currently, the labelling of many peptide–chelator conjugates is performed at high temperature, while monoclonal antibodies withstand heating only to 37 °C. Hence, preferable ligands are those that form complexes within a few minutes at temperatures below 37 °C.

3.1. Complexes with DOTA-based ligands and related macrocyclic chelators

Many clinically used radiopharmaceuticals contain the aza crown DOTA (**3**), which is the gold standard for many cations of radionuclides.[6] Complexes with DOTA are characterized by high thermodynamic (see Table 3) and kinetic stability; however, the binding rate of this ligand to cations

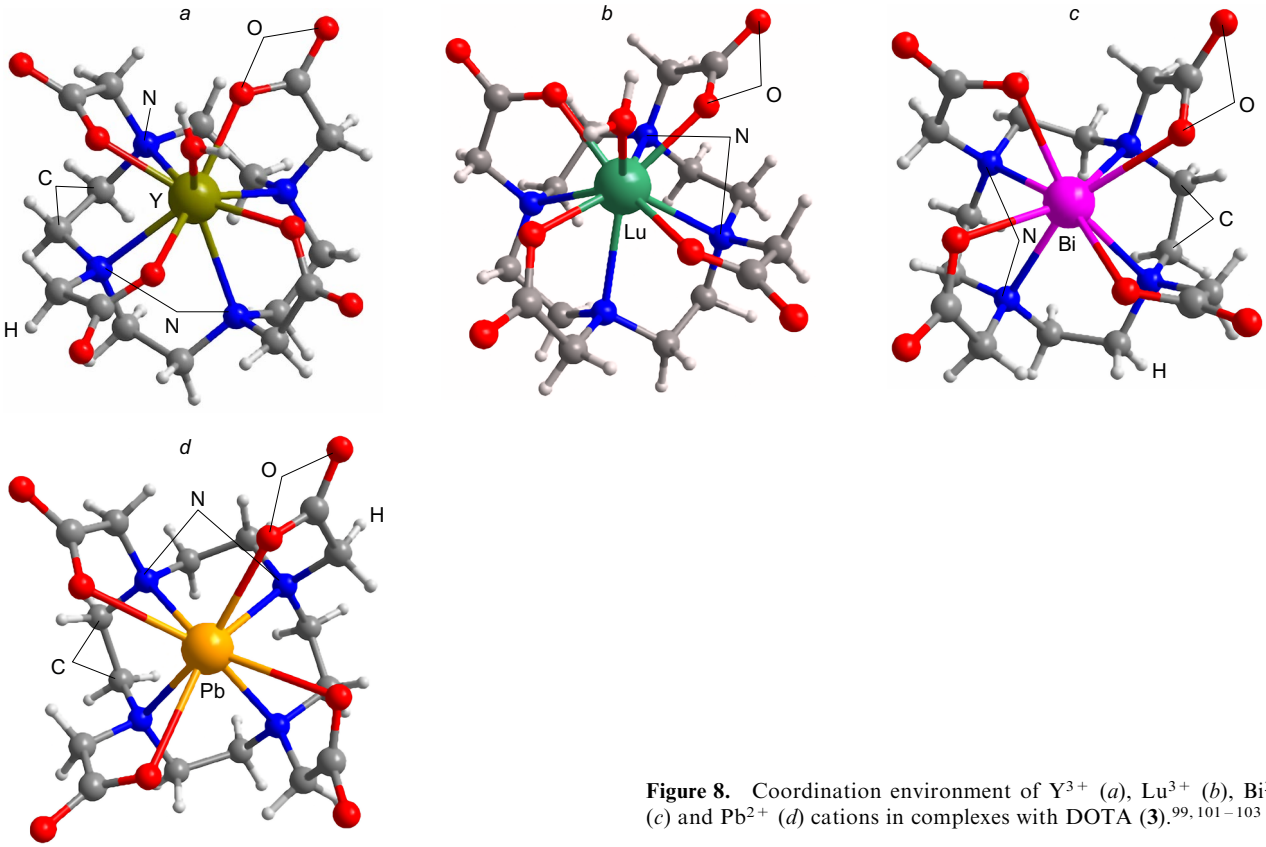
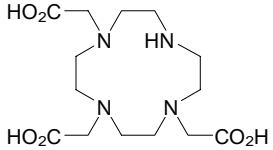


Figure 8. Coordination environment of Y^{3+} (*a*), Lu^{3+} (*b*), Bi^{3+} (*c*) and Pb^{2+} (*d*) cations in complexes with DOTA (**3**).[99, 101 – 103]

is slow and the complexation occurs at elevated temperature. Ligand **3** is the most appropriate ligand for binding to triply charged REE cations and Bi^{3+}. Figure 8 displays the structures of Y^{3+}, Lu^{3+}, Bi^{3+} and Pb^{2+} complexes with DOTA.[99, 101 – 103]

The coordination polyhedron of REE^{3+} cations (CN 9) in complexes with DOTA (**3**) is a square prism or antiprism, depending on the size of the cation,[104, 105] that is formed by four amino groups and four carboxyl groups and is capped with a water molecule (see Fig. 8 *a*,*b*). The cation is located above the plane of the macrocycle and carboxyl groups are in *syn* positions.[101, 105 – 107] In complexes with the Bi^{3+} cation,[99] the highest possible coordination number of which is 8, the additional coordinated water molecule is absent (see Fig. 8 *c*). The coordination polyhedron of the Pb^{2+} cation in complexes with DOTA (**3**)[103] can be described as a distorted square prism capped with a water molecule (see Fig. 8 *d*); however, the coordination environment is highly asymmetric [Pb – O bonds are elongated from 2.61 to 2.86 Å; the Pb – N bonds, from 2.64 to 2.69 Å)] due to the presence of the stereochemically active lone pair of Pb^{2+}. It should be noted that such asymmetry is not observed in complexes of Bi^{3+}, which also has a lone pair, with DOTA (**3**) and its analogue DO3A (**9**).[108] Thus,

Structure 9



9 (DO3A)

the Bi – O and Bi – N bonds are shorter and vary in a narrower range (2.49 – 2.58 Å) although, according to quantum chemical calculations, the lone pair of Bi^{3+} in these complexes is also stereochemically active.[108]

An analysis of the crystallographic data for complexes of a series of REEs with DOTA (**3**) shows that there is a reverse correlation between the distance from the cation to N atoms of the macrocyclic cavity and the stability constant of the complexes in solution. Thus, the smaller the M – N distance, the larger $\log K_{ML}$.[109]

Quantum chemical calculations demonstrated that the low binding rate of the cation to ligand **3** is attributed to the gradual deprotonation of amino groups with the simultaneous incorporation of the cation into the cage formed by carboxyl and amino groups.[110] This complexation mechanism was experimentally confirmed by Moreau *et al.*[111] They proved the formation of protonated intermediates M – H_2DOTA [doubly protonated at amino groups of DOTA (**3**); the complexation occurs only at carboxyl groups] and M – HDOTA (dissociation of H^+ from the amino group and the migration of the cation inside the cage). These complexes are formed in the course of the gradual incorporation of the cation into the cage. The complexation is accompanied by changes in the bond lengths and the number of water molecules in the hydration shell of the cation, which were monitored by luminescence spectroscopy and extended X-ray absorption fine structure (EXAFS) spectroscopy of the Eu-DOTA, Gd-DOTA, and Tb-DOTA complexes. These data provide an explanation for the earlier results of optimization of the synthesis conditions for RPs involving DOTA (**3**).[112] Thus, an increase in the pH value leads to a proportional decrease in the time required for the quantitative binding of ^{90}Y to

the MAb–ligand **3** conjugate. An increase in pH results in an increase in the percentage of the deprotonated form of DOTA, which efficiently binds the radionuclide. The dissociation of M-DOTA in an acidic medium was described.[113] It involves the protonation of a carboxyl group, the proton migration to the amino group of the macrocycle and the M–N bond cleavage.

Experimental studies of the dissociation of complexes at pH 2 showed that the percentage of Y^{3+}, Sm^{3+} and Lu^{3+} cations that remain bound to the ligands DOTA (**3**) and CHX-DTPA (**6**) within 5 days is 90%–100%, whereas the percentage of these ions coordinated by DTPA (**2**) is only 15%.[114, 115] The Ac^{3+} cation, as a chemical analogue of REEs, also forms the most stable complexes with DOTA (**3**); 90%–100% of the labelled ^{225}Ac-DOTA-MAb conjugates remain intact in the blood serum over 10 days.[116]

As can be seen in Table 4, the rapid complexation with DOTA (**3**) is possible only at elevated temperature, at which the deprotonation occurs more easily. The yield of the DOTA labelling reaction depends on many factors, including the ligand concentration, the pH value of the reaction mixture, the temperature and the duration of heating, and also on the presence of impurity cations.[115, 117] In some cases, when the MAb bioconjugate cannot withstand heating, an Ac^{3+} complex with DOTA (**3**) was initially synthesized at 56 °C followed by the conjugation of the radioactive complex to immunoglobulins.[116]

Table 4. Synthesis conditions of selected labelled DOTA (**3**)-based conjugates.

Labeled conjugate	Synthesis conditions			Ref.
	pH (buffer)	T/°C	time /min	
^{90}Y -DOTA-MAb	pH 7–7.5 (NH_4OAc)	37	30	112
^{90}Y -DOTATATE	–	95	25	27
^{90}Y/^{177}Lu-DOTA-cG250(MAb) [a]	pH 5.4 (NH_4OAc)	45	60	118
^{213}Bi-DOTATOC	pH 6–7 (NH_4OAc)	100	5	119
^{213}Bi-DOTA-PESIN [b]	pH 8.5–8.7 (Na_2CO_3)	95	5	120
^{212}Pb-DOTA-Re(Arg11)CCMSH [c]	pH 5.4 (NH_4OAc)	75	40	87

[a] cG250(MAb) is chimeric MAb against renal cancer cells; [b] PESIN is a peptide specific for prostate carcinoma cells; [c] Re(Arg11)CCMSH is a peptide specific for melanoma cells.

An elongation of alkylene bridges from ethylene ones in macrocyclic DOTA (**3**) to propylene bridges in the ligand 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid (TETA, **10**) allows the formation of six-membered rings upon coordination of the cation, and these rings, like five-membered rings, are responsible for stability of the resulting complexes. However, the stability constants of REE complexes with ligands **10** and **3** of the same denticity are significantly different, the constants with the former ligand being ten orders of magnitude lower than those of the corresponding complexes with ligand **3**. It should be noted that all resulting complexes have similar structures. The coordination polyhedron is a square antiprism with carboxyl groups in *syn* positions (Fig. 9),[121] but the macrocycle in complexes with TETA is much more distorted compared to DOTA due to coordination of nitrogen atoms. This is apparently the factor responsible for lower stability, both thermodynamic and kinetic, of REE-TETA complexes compared to REE-DOTA.[122]

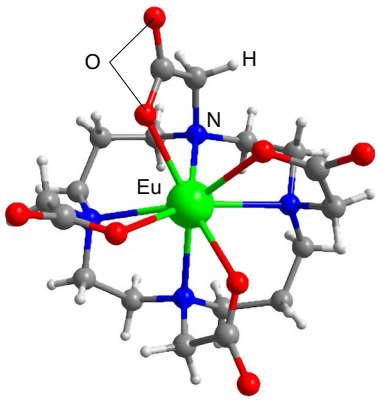
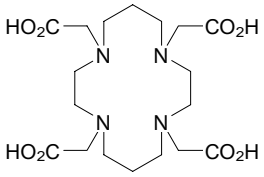


Figure 9. Coordination environment of the Eu^{3+} ion in the complex with TETA (**10**).[121]

Structure 10



10 (TETA)

The same conclusion can be made for Bi-TETA and Pb-TETA complexes. The assessment of stability of these complexes in acid solution showed that these complexes are unstable in the presence of 0.01 M acid, whereas Bi-DOTA does not dissociate even in a 1 M solution at least over one month.[123]

The Pb-DOTA complex is slowly decomposed in the presence of an acid. Hence, this complex can be considered as stable taking into account the half-life of ^{212}Pb.[123] The further investigation of the radioactive ^{212}Pb-DOTA complex demonstrated that β-decay of ^{212}Pb in the complex with DOTA led to release of 36% of ^{212}Bi.[124] This fact was confirmed by *in vivo* experiments in leukemia-bearing mice, where the accumulation of ^{212}Bi in the kidneys was observed.[125] In this case, the dissociation of the complex is associated not so much with the recoil energy of daughter ^{212}Bi after β-decay of ^{212}Pb (0.5–2.3 eV; 12–55 kcal mol^{-1}) as with the generation of the highly ionized Bi^{5+} cation[124] due to emission of a cascade of conversion and Auger electrons. The latter are produced by γ-radiation that accompanies β-decay of ^{212}Pb. The overall probability of γ-radiation from ^{212}Pb is 37%, which is consistent with the release of 36% of ^{212}Bi from the complex. Liposomes were also tested as carriers for ^{212}Pb, and the resulting systems [the cation incorporated into a liposomal vesicle functionalized with DOTA (**3**)] were shown to be stable in the serum at 37°C.[126]

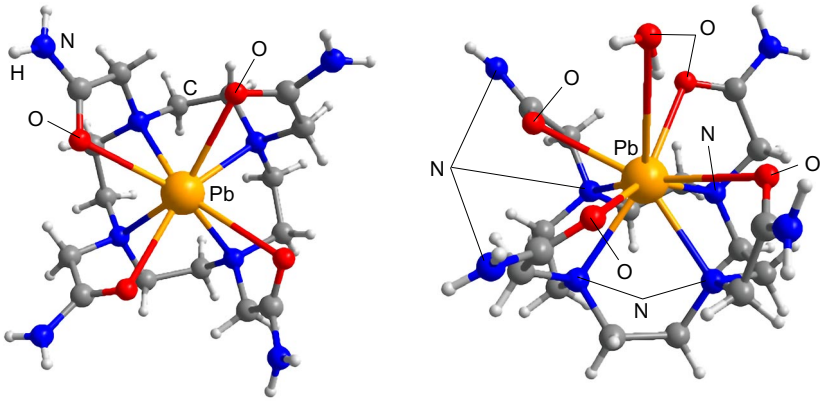


Figure 10. Coordination environment of the Pb^{2+} ion in the complex with TCMC (**8**).[129]

A DOTA analogue, TCMC (**8**), in which carboxyl groups were replaced with amide groups, was synthesized in order to address the problem of acid dissociation of the complex containing the Pb^{2+} cation. The presence of amide groups leads to a decrease in the overall protonation constant of this ligand ($\Sigma pK_a = 13.9$),[127] thereby facilitating a decrease in the rate of dissociation of the complex in an acidic medium at pH 2 – 3 compared to DOTA (**3**).[128] Thermodynamic stability of the Pb-TCMC complex ($\log K_{Pb\text{-}TCMC} > 19$)[127] is comparable with that of Pb-DOTA ($\log K_{Pb\text{-}DOTA} = 22.7$).

Stability of the Bi-TCMC complex was not evaluated. However, it can be suggested that the stability constant of this complex is comparable with that of the Pb^{2+} complex taking into account similar hardness of these cations (see Table 2). For harder REE cations, which are coordinated through carboxyl groups, the binding constants to TCMC are much lower than those to DOTA ($\log K_{La\text{-}TCMC} = 10.4$).[127] The coordination polyhedron of Pb^{2+} in the complex with TCMC, like that in the complex with DOTA, can be described as a distorted square antiprism with a site for the localized lone pair (Fig. 10).[129] Ligand **8** is currently used in clinical trials of ^{212}Pb-labelled RPs conjugated to antibodies as agents for the therapy of ovarian and abdominal cancer.[89,90] The latter fact was mentioned in the previous section.

The ligand TCMC (**8**) provides more efficient binding of ^{212}Pb to a conjugate compared to DOTA. Thus, TCMC enables >95% binding of the isotope at 37 °C within 30 min, while DOTA (**3**) ensures 60% – 80% chelation under the same conditions. A higher rate of complexation with ligand **8** compared to DOTA (**3**) can be employed for the rapid secondary chelation of the released Bi^{3+} cation *in vivo*, which is impossible with DOTA.[6,72,98]

However, the binding of REE cations to ligand **8** is a slow process.[130] The cation is bonded to the fully deprotonated ligand rather than to the partially deprotonated ligand as observed for DOTA (**3**). This fact is attributed to the absence of a zwitterion in the former case. In this case, the proton can rapidly transfer from the carboxyl group to the amino one and back, because the amide groups are protonated only in a strongly acidic medium. The rate of bond formation with carbonyl groups is determined by the rate of dehydration of the cation. Stenson *et al.*[131] succeeded in growing a crystal of the intermediate complex [Gd-TCMC · 4 H_2O]. The coordination sphere of the cation in this complex involves four carbonyl groups of TCMC and four water molecules (Fig. 11). The transformation of the intermediate into the final complex [Gd-TCMC · H_2O], the cation of which is completely encapsulated in the macrocyclic cage of the ligand (see Fig. 11 *b*),[132] requires that not only the ligand be fully deprotonated but also water molecules be displaced from the inner sphere of the cation. Correspondingly, the rate of exchange of water molecules in the coordination sphere of Ln^{3+} is one of the rate-limlting factors for the formation of the Ln-TCMC complex. An analysis of the bond lengths shows that the distance between the *trans*-carbonyl oxygen atoms in [Gd-TCMC · 4 H_2O] is smaller than that in [Gd-TCMC · H_2O], Hence, the transition between these two configurations is hindered. The calculated stability constants of REE complexes with TCMC

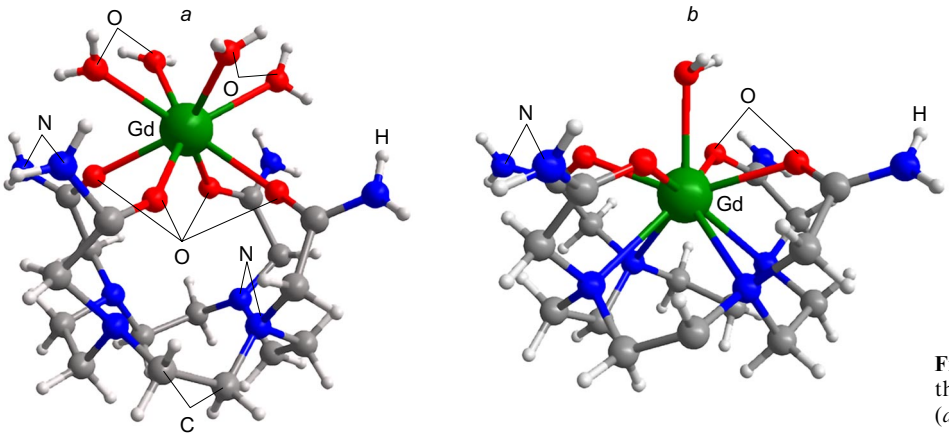
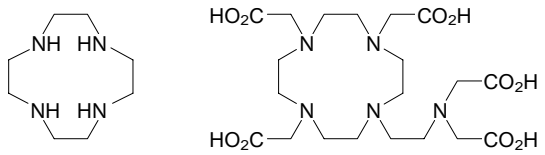


Figure 11. Molecular structures of the complexes [Gd-TCMC · 4 H_2O] (*a*) and [Gd-TCMC · H_2O] (*b*).[131,132]

($\log K_{\text{Ln-TCMC}} = 10-11$)[133] are ten orders of magnitude lower than $\log K_{\text{Ln-DOTA}}$ (Table 3). However, REE complexes with TCMC very slowly dissociate in an acidic medium ($T_{1/2} = 50$ days) and in the presence of excess competing Cu^{2+} cations.[134] Like the formation of complexes with DOTA, the slow complexation of REEs with TCMC correlates with high stability *in vitro*.

The low rate of complexation under ambient conditions is a critical parameter and, correspondingly, this is the main drawback of DOTA hindering its widespread use as a chelating agent in RPs for many radionuclides. Since the stability of complexes with DOTA directly correlates with the incorporation of the cation in the macrocyclic cage, the preservation of the crown cavity is necessary for the preparation of kinetically stable complexes. The introduction of additional chelating groups can increase the binding rate, and the stability of the resulting complexes will be determined by the presence of a macrocyclic cyclen molecule (**10**) similar to DOTA (**3**). One of the promising modified agents is the chelator {7-[2-(bis(carboxymethyl)-amino)ethyl]-4,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl}acetic acid (DEPA, **11**).

Structures 10, 11



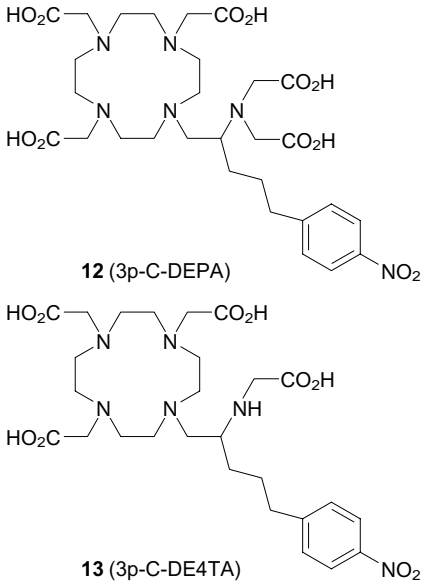
10 (cyclen) **11** (DEPA)

This ligand is an analogue of DOTA (**3**), in which one carboxyl group is replaced with the aminodiacetyl moiety, resulting in total in 10 coordinating donor atoms per ligand molecule. As a result, the backbone of DEPA is less rigid, thereby enabling efficient binding of Bi^{3+} (at pH 4), ^{90}Y and ^{177}Lu (at pH 5.5) cations within 5 min at room temperature.[135, 136] The coordination polyhedron in this complex is a square antiprism.[6] Thermodynamic data on the stability constants of these ligands with cations are lacking in the literature.

Due to a large number of donor groups in DEPA (**11**) for coordination of REE cations with small ionic radii [for CN 9, $R(Y^{3+}) = 1.075$ Å, $R(Lu^{3+}) = 1.032$ Å],[21] the complexation is reversible and radionuclide – MAb conjugates are unstable. For instance, RP based on M^{3+}-3p-C-DEPA-trastuzumab (3p-C-DEPA, **12**) loses 30% – 50% of ^{90}Y and ^{177}Lu isotopes in the blood serum.[137] Apparently, the smaller the number of donor atoms, the higher stability of the complexes. Actually, the ligand 3p-C-DE4TA (**13**) possessing nine donor atoms forms complexes with Y^{3+} and Lu^{3+} characterized by high stability in the blood serum,[136] the complex with Y^{3+} being the most stable one due to the larger ionic radius of this cation.

Unlike complexes of DEPA (**11**) with REE cations, the complex with Bi^{3+} is stable *in vitro* in the blood serum for 14 days,[135] as was confirmed by *in vivo* experiments. In studies in laboratory animals, no radioactivity uptake in organs was observed. Thus, the maximum value of 2.44% injected dose per gram of organ (ID/g) is achieved in the kidneys within the first half hour and then it decreases to 0.4% ID/g in the kidneys and spleen after 24 h. Upon

Structures 12, 13



12 (3p-C-DEPA)

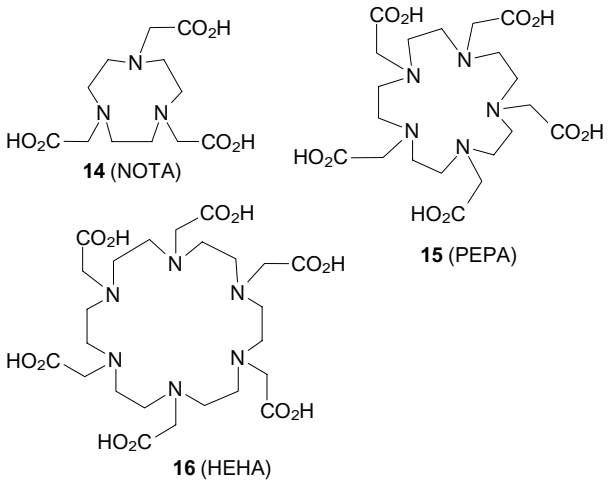
13 (3p-C-DE4TA)

further conjugation to the MAb trastuzumab,[138] a high rate of complexation (90.4% of the isotope was bound within 5 min) and kinetic stability in the serum (after storage for 72 h, 100% of Bi^{3+} remained in the conjugate) are retained.

Experiments in laboratory colon tumour-bearing animals[139] showed that after the injection of $^{205/206}$Bi-(3p-C-DEPA)-trastuzumab and $^{205/206}$Bi-(C-DOTA)-trastuzumab, the same distribution of $^{205/206}$Bi in organs was observed, and radionuclides were gradually accumulated in the tumour for 24 h: the uptake in the tumour was 26% – 27% ID/g; the uptake in the liver and kidneys 7% – 8% ID/g. This fact indicates that the complexes with DEPA and DOTA have the same kinetic stability.

The following DOTA analogues with larger and smaller crown cavities were tested: 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA, **14**), 1,4,7,10,13-pentaazacyclopentadecane-1,4,7,10,13-pentaacetic acid (PEPA, **15**) and 1,4,7,10,13,16-hexaazacyclohexadecane-1,4,7,10,13,16-hexaacetic acid (HEHA, **16**).

Structures 14 – 16



14 (NOTA)

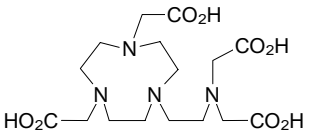
15 (PEPA)

16 (HEHA)

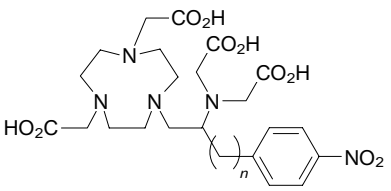
Like EDTA, the chelator NOTA (**14**) with a smaller macrocycle contains only six donor atoms for coordination of a cation. However, the stability constants of REE complexes with NOTA are 2 – 3 orders of magnitude lower than those of the complexes with EDTA.[140] It was shown that complexes with light-group REE cations (La – Gd) have approximately equal stability ($\log K = 13 - 14$). Then $\log K_{\text{M-NOTA}}$ monotonically increases with increasing charge density on the cation. In the case of small macrocycles, light lanthanides with larger ionic radii cannot be coordinated simultaneously by all heteroatoms of the macrocycle and chelating substituents, resulting in the formation of penta- and hexadentate complexes. The presence of two types of complexes was confirmed by ^{1}H and ^{13}C NMR spectroscopy[141] and time-resolved Eu^{3+} luminescence spectroscopy.[142] The rate of complexation with NOTA (**14**), like that with DOTA (**3**), is determined by the gradual incorporation of the cation into the cage between the macrocycle and carboxyl groups, while the dissociation proceeds in a reverse order.[143]

The ligand NETA (**17**)[144] and its bifunctional analogue 3p-C-NETA (**18a**) were prepared by introducing additional binding sites into NOTA (**14**). Due to an increase in the number of coordination sites, REE and Bi^{3+} complexes with NETA (**17**) do not dissociate in the blood serum and *in vivo*.[145] The complexation time at 25 °C is 20 min for Lu^{3+} and 10 min for Bi^{3+}, whereas the complexation time for DOTA (**3**) is 1 h.[146] Biodistribution studies of complexes with NETA (**17**) in healthy mice showed that the radionuclide is rapidly excreted from the body *via* kidneys. Besides, no ^{90}Y uptake in bones was observed in experiments with ^{90}Y-NETA.[144, 145] This is indirect evidence that Y^{3+} does not dissociate, because it is accumulated in bones only in the free state.[147] The conjugation of NETA (**17**) to the MAb trastuzumab [M^{3+}-3p-C-NETA-trastuzumab (**18a**)] affects neither the kinetics of complexation (95% – 99% of ^{177}Lu, ^{90}Y and $^{205/206}Bi$ were bound within 5 min) nor stability of the resulting complex in the blood serum.[137, 148] However, the administration of the targeting agent ^{177}Lu-(3p-C-NETA)-trastuzumab to breast cancer-bearing mice resulted in a gradual accumulation of the radionuclide in the tumour with a simultaneous decrease in radioactivity in other organs and blood, but the maximum uptake in the tumour was 10% ID/g,[137] which may be due to the effect of the chelating agent on the affinity of the antibody.

Structures 17, 18



17 (NETA)



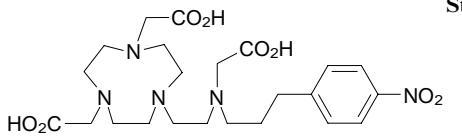
n = 3 (**a**), 5 (**b**)

18a,**b** (np-C-NETA)

In order to reduce the effect of the chelator on the affinity of its conjugates to cancer cell receptors, Kang *et al.*[149] synthesized the ligand 5p-C-NETA (**18b**) with a longer alkyl chain in the acyclic moiety compared to NETA that is used for covalent conjugation to a peptide.[149] The *in vivo* distribution in glioblastoma-bearing mice confirmed the specificity of the administered agent ^{177}Lu-(5p-C-NETA)-RGDyK to cancer cells (RGDyK is a cyclic pentapeptide that has affinity to many cancer cell receptor, including breast cancer, prostate cancer and glioblastoma receptors). It was shown that a low, through persistent, radioactivity (1% – 1.5% ID/g) is present in the tumour, while it monotonically decreases in the kidneys from 3% to 1% ID/g within 24 h. Apparently, the low uptake in the tumour is associated with a decrease in the specific activity of the agent. This activity is 65 mCi per milligram of peptide (mCi mg^{-1}) for ^{177}Lu-(5p-C-NETA)-RGDyK, whereas it is 482 mCi mg^{-1} for ^{177}Lu-(3p-C-NETA)-RGDyK. This fact is attributable to a higher tendency of the conjugate with a long alkyl chain to aggregation, thereby decreasing the yield of the labelling reaction.

As opposed to Y^{3+} and Lu^{3+} complexes with ligand **18a**, which are equally stable *in vitro*, a decrease in the number of donor atoms in 3p-C-NE3TA (**19**) results in different stability of its complexes with these cations in the presence of serum proteins. Thus, 98% of Lu^{3+} and 65% of Y^{3+} were bound in complexes after 7 days. The synthesis of REE complexes with 3p-C-NE3TA (**19**) at room temperature requires a long time for completion. For instance, the chelation of 95% of Lu^{3+} is completed within 60 min, whereas only 69% of Y^{3+} are bound during this period of time. Higher stability of the Lu^{3+} complex is attributed to the smaller ionic radius of this cation, which fits the size of macrocycle **19**.[136] Despite the equally high *in vitro* stability of Lu^{3+} complexes, biodistribution studies in healthy mice showed that the administration of ^{177}Lu-(3p-C-DE4TA) and ^{177}Lu-(3p-C-NE3TA) leads to a significant radioactivity uptake in the liver (7% – 17% ID/g), whereas the radioactivity uptake evaluated in the parallel experiment for ^{177}Lu-(3p-C-NETA) is as low as 1.5% ID/g. Apparently, in the latter case a decrease in the number of chelating groups in the ligand leads to a decrease in stability manifested in *in vivo* conditions.

Structure 19



19 (3p-C-NE3TA)

To the best of our knowledge, data on the thermodynamic stability constants of complexes with the ligands NETA (**17**) and NE3TA (**19**) are lacking in the literature.

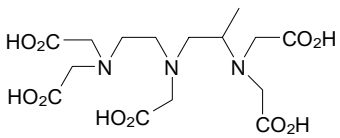
The thermodynamic stability of complexes with other analogues of DOTA (**3**), namely PEPA (**15**) and HEHA (**16**), was evaluated for all REEs.[150] For ligands **15** and **16**, the constants increase with decreasing ionic radius of the cation in the series $La^{3+} \rightarrow Lu^{3+}$: $\log K_{\text{M-PEPA}} = 13.6 \rightarrow 16.7$ and $\log K_{\text{M-HEHA}} = 19.1 \rightarrow 24.3$. Stability of the complexes with HEHA (**16**) is similar to that of the complexes with DOTA (see Table 3). However, HEHA (**16**) binds the cations 100 times faster than DOTA

(**3**) due to a relatively higher flexibility of ligand **16** but 10 times more slowly than DTPA (**2**). A comparison of the efficacy of acyclic and macrocyclic chelators for Ac^{3+} *in vivo* showed that the Ac-HEHA complex is characterized by the faster clearance from the body and the lower activity uptake in the liver and kidneys compared to related complexes with EDTA, DTPA (**2**), CHX-DTPA (**6**) and DOTA (**3**).[151] However, upon conjugation of HEHA (**16**) to MAb, the Ac^{3+} complex proved to be unstable, with the result that less than 50% of Ac^{3+} was bound in the complex after 24 h.[128]

3.2. Complexes with acyclic ligands

The ligand DTPA (**2**), like DOTA (**3**), forms stable complexes with many cations (see Table 3). The complexation occurs at room temperature within a few minutes.[152] A comparison of the chelators analogous to DTPA (**2**) and DOTA (**3**) showed that the chelation with ligand **2** and its derivatives CHX-DTPA (**6**), MX-DTPA (**20**) occurs more rapidly, and the presence of traces of impurity metals (Ca^{2+}, Fe^{2+}, Zn^{2+}) has almost no effect on the complexation, as opposed to the complexation with DOTA (**3**).[114,115] However, complexes with DTPA (**2**) are characterized by rapid dissociation in acidic media, in the presence of serum proteins[115,153,154] and *in vivo*, resulting in the uptake of free Y^{3+} cations in bones[155] and of Bi^{3+} in the kidneys.[156] For example, a *in vivo* comparison of ^{206}Bi-labelled DTPA (**2**) and DOTA (**3**) conjugated to MAbs showed that 9% ID/g of ^{206}Bi-DTPA-MAb and 90% ID/g of ^{206}Bi-DOTA-MAb were present in the tumour tissue after 1 h, while the uptake of these conjugates in the kidneys was 80% and 12% ID/g, respectively.[156]

Structure 20



20 (MX-DTPA)

The coordination polyhedron in REE complexes with DTPA (**2**), like that in the complexes with DOTA, is a square antiprism capped with a water molecule (Fig. 12 *a*).[157] The structures of Bi^{3+} complexes, with the completely deprotonated ligand (see Fig. 12 *b*)[158] and with the diprotonated ligand (see Fig. 12 *c*)[159] were described in the literature. In both these complexes (see Fig. 12 *b*,*c*), the carboxyl oxygen atom of the second ligand is coordinated to the cation. Besides, one of the two protonated carboxyl groups of the ligand in the Bi-H_2DTPA complex (see Fig. 12 *c*) is involved in the complexation, while the second carboxyl groups points away from the cation, resulting in one unoccupied vertex of the coordination polyhedron of the cation (antiprism), as opposed to Bi-DTPA (see Fig. 12 *b*).[159] Complexes with DTPA are labile in aqueous solutions, which is attributed, *inter alia*, to the coordination of two ligand molecules. Since intermolecular interactions in solution are weaker than in crystals, the cation is not fully shielded from surrounding solvent molecules once the crystal lattice is destroyed.[159]

To decrease the dissociation rate of complexes with DTPA (**2**), methyl- and cyclohexyl-containing DTPA derivatives **21**–**25** were synthesized.[155,160,161] These moieties provide the preorganization of the structure for metal cation binding. The data on thermodynamic stability of complexes with DTPA derivatives were not systematically considered in the literature. The only known fact is that $\log K_{ML}$ for complexes with DTPA (see Table 3) and some its derivatives have similar values, *e.g.*, $\log K_{Bi\text{-}CHX\text{-}DTPA} = 34.9$[100] and $\log K_{Y\text{-}CHX\text{-}DTPA} = 24.2$.[162]

Complexes of REE and Bi^{3+} cations with the ligands CHX-DTPA (**24**, **25**) are much more stable than complexes with ligands **2** and **1** [1B4M-DTPA, also known as tiuxetan, used in the drug Zevalin® (Refs 155, 160, 161)]. In an acidic medium at pH 2, the ^{90}Y-(CHX-DTPA) complex undergoes 30% dissociation overnight, whereas the ^{90}Y-DTPA complex is 80% dissociated.[114] In *in vivo* biodistribution studies of the ^{206}Bi-(CHX-DTPA) complex, the kidney uptake was 8%–9% ID/g 6 h after the administration,[161] which is in agreement with the data for the Y^{3+} cation,[155] whereas the uptake of 13–30% ID/g was observed for derivatives **1** and **21**–**23**. The latter data confirm higher *in vivo* stability of complexes with CHX-DTPA compared to DTPA.

High stability of the Bi-(CHX-DTPA) complex is associated with its structural characteristics.[159] The coordination polyhedron is a square antiprism (Fig. 13) with all eight vertices being occupied by heteroatoms and chelating groups of one CHX-DTPA molecule. The Bi^{3+} cation has a similar coordination environment in the Bi-DTPA (see Fig. 12 *b*), Bi-(CHX-DTPA) (see Fig. 13) and

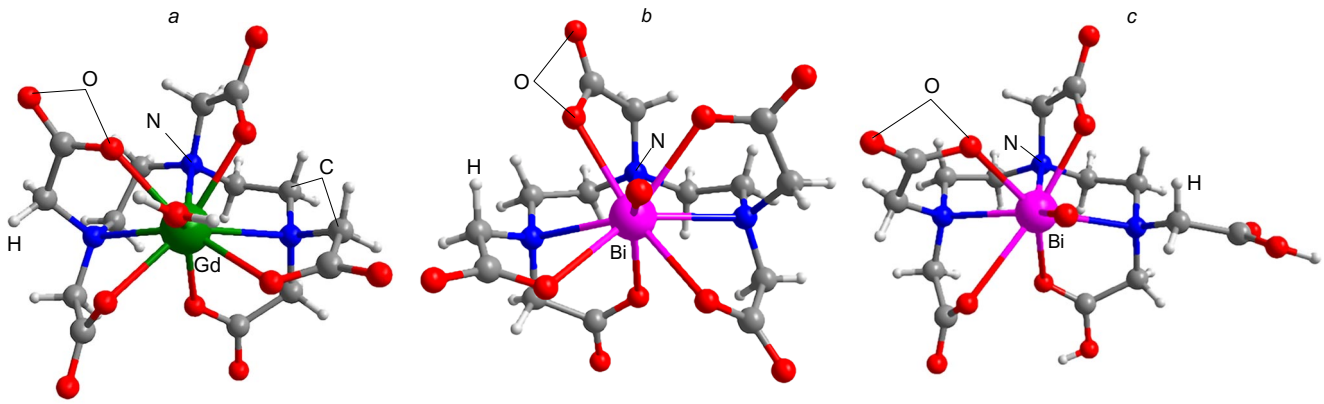
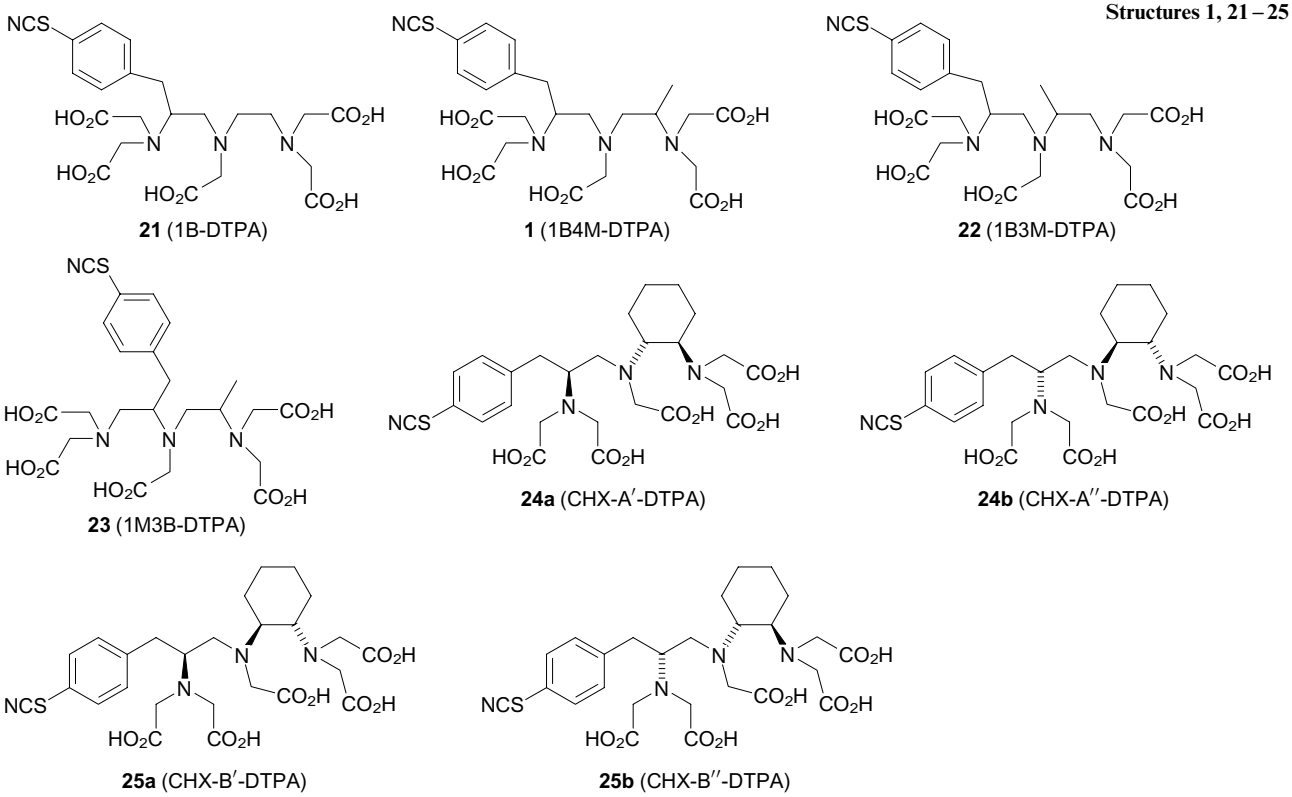


Figure 12. Molecular structures of the Gd-DTPA (*a*),[157] Bi-DTPA (*b*)[158] and Bi-H_2DTPA (*c*) complexes.[159]

Structures 1, 21 – 25



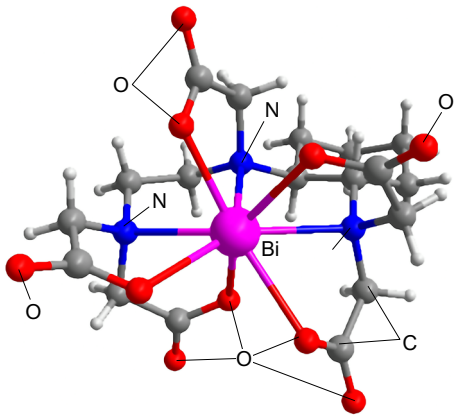


Figure 13. Molecular structure of the Bi-(CHX-DTPA) complex.[159]

Bi-H_2DTPA complexes; however, the Bi—O and Bi—N bond lengths in these complexes are in the ranges of 2.29 – 2.72, 2.37 – 2.69 and 2.37 – 2.61 Å, respectively. The Bi-(CHX-DTPA) complex is characterized by the narrowest range and smallest values of interatomic distances apparently due to the preorganization of CHX-DTPA for coordination of the cation.

A comparison of the conditions of the preparation and *in vitro* and *in vivo* stability of ^{90}Y complexes with the ligands DOTA (**3**), CHX-DTPA (**24**, **25**) and DTPA (**2**)[163] provides additional evidence that the complex with ^{90}Y-(CHX-DTPA) is most suitable for the application regarding its most important parameters (efficiency of radionuclide binding, stability of complexes in the presence of other cations and in serum, *in vivo* distribution). This complex persists in the serum (by 96%) for 24 h, and 80% – 100% of the complex remains intact in the presence of a 1000-fold excess of Fe^{3+}, Cu^{2+}, Zn^{2+} and Ca^{2+} ions, whereas only 30% – 40% of complexes with DOTA (**3**) remain intact under similar conditions.

The ligand CHX-DTPA can be represented by two enantiomers (CHX-A-DTPA and CHX-B-DTPA). The ligand p-SCN-Bn-CHX-DTPA containing a bifunctional moiety is a diastereomer and has four optical isomers (**24a**,**b** and **25a**,**b**). The REE complexes with CHX-A-DTPA (CHX-A′, CHX-A″) and CHX-B-DTPA (CHX-B′, CHX-B″) are characterized by different kinetic stability both *in vitro* and *in vivo*.[155, 161, 162, 164] The complexes within the CHX-A and CHX-B groups are characterized by similar dissociation behaviour in the blood serum [0.3%/day for ^{88}Y-(CHX-A-DTPA) *versus* 1.3%/day for ^{88}Y-(CHX-B-DTPA)] and similar *in vivo* behaviour (the ^{88}Y uptake in bones during 7 days is 4% – 22% ID/g for CHX-B and 2% – 5% ID/g for CHX-A).[164] The thermodynamic stability constants of REE complexes with isomers **24** and **25** have similar values: $\log K_{Y\text{-(CHX-A-DTPA)}} = 24.7$ and $\log K_{Y\text{-(CHX-B-DTPA)}} = 24.4$.[162] It is evident that the preorganization of the ligand structure affects stability of their complexes *in vitro* and *in vivo*. Thus, due to the orientation of donor groups more convenient for the cation coordination, CHX-A-DTPA (**24**) forms stable complexes in biological media.

For the ^{206}Bi-CHX-DTPA complex, no differences in the radioactivity distribution depending on the enantiomer used were found.[161] Besides, it was shown that both complexes remain conjugated to monoclonal antibodies for at least 6 h, which is equal to six half-lives of the ^{212}Bi isotope.[160]

Table 5. Synthesis conditions of CHX-DTPA-based ^{86}Y-labelled conjugates.

Labelled conjugate	Synthesis conditions			Ref.
	pH (buffer)	T/°C	time /min	
^{86}Y-(CHX-A″-DTPA)-MAb	7 (NH_4OAc)	rt	30	165
^{88}Y-(CHX-A″-DTPA)-B3(MAb) [a]	6 (NH_4OAc)	rt	30	164
^{86}Y-(CHX-A″-DTPA)-panitumumab [b]	7 (NH_4OAc)	rt	30	166
^{86}Y-(CHX-A″-DTPA)-MAb	5.6 (NH_4OAc)	rt	60	167
^{86}Y-(CHX-A″-DTPA)-ReCCMSH(Arg11) [c]	5.5 (NH_4OAc)	75	30	168

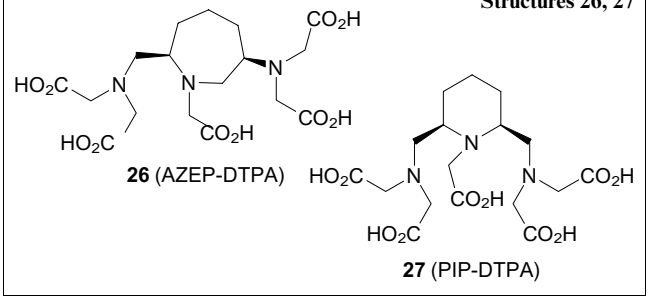
[a] B3(MAb) is MAb against many cancer cells; [b] panitumumab is MAb against epidermal growth factor receptors expressed by membranes of many cancer cells, including colorectal cancer cells; [c] ReCCMSH(Arg11) is a peptide specific for melanoma cells.

Therefore, the enantiomeric purity is important requirement for the ligands CHX-DTPA. If RPs are synthesized using a racemate, a large percentage of the complex will undergo much more rapid *in vivo* dissociation, and this can lead to undesirable biodistribution.[6]

Slow dissociation of complexes with CHX-DTPA (off rate) is directly related to a low binding rate (on rate), as in the case with DOTA (**3**)-containing complexes. Therefore, labelled bioconjugates based on CHX-DTPA are synthesized during 30 – 60 min at elevated temperatures (Table 5).

Apart from CHX-DTPA (**24**, **25**), the following derivatives of DTPA (**2**) with other cyclic substituents in the backbone were studied: AZEP-DTPA (**26**) and PIP-DTPA (**27**).[169] In the series of Y^{3+}, Lu^{3+}, Bi^{3+} and Pb^{2+} complexes with these ligands, the Y-(AZEP-DTPA) complex is the least stable one in serum. The dissociation of this complexes reaches 32% within 11 days. Complexes with other cations are stable for a longer time. The following data on radionuclide uptake are available: ⩽10% ID/g in bones [^{86}Y-(AZEP-DTPA)], ⩽10% ID/g [(^{203}Pb-(AZEP-DTPA)] and ⩽15% ID/g [^{206}Bi-(AZEP-DTPA)] in the kidneys.

Structures 26, 27



Comparative *in vivo* studies of acyclic and macrocyclic ligands conjugated to monoclonal antibodies were performed [170 – 172] in order to choose an appropriate chelator for RPs. Complexes with DOTA (**3**) and CHX-A-DTPA (**24**) have higher kinetic stability compared to complexes with other functionalized DTPA derivatives.[115, 162]

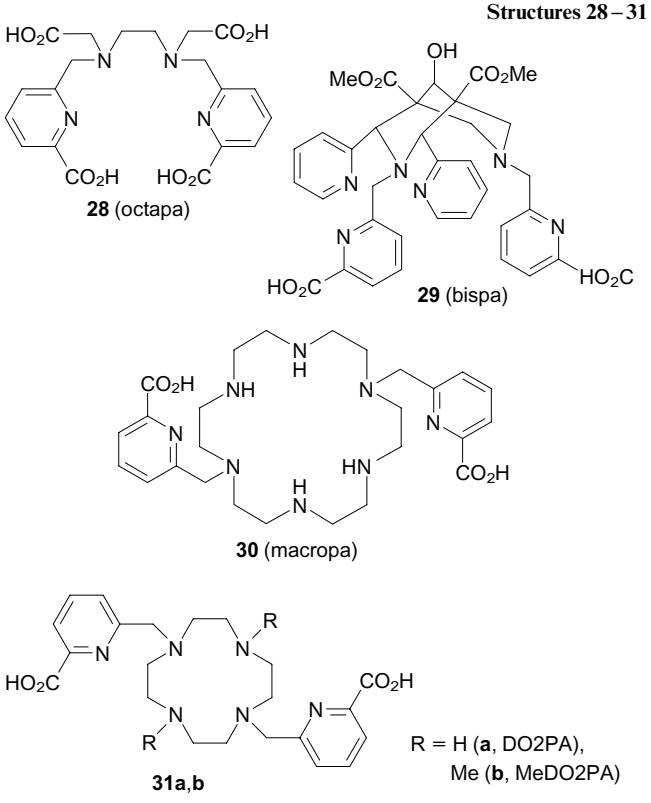
3.3. Complexes with ligands containing pyridine and benzene moieties

In the field of research on macrocyclic and acyclic ligands, ligands containing aromatic and heteroaromatic moieties,[173 – 176] which can be involved in macrocycles and act as additional chelating groups, have attracted growing interest in recent years.

A picolinate moiety, which combines a pyridine ring and a carboxyl group is currently a popular chelator. The presence of donor nitrogen and oxygen atoms with a fixed distance between them provides an additional stabilizing effect outside the backbone of ligands **28** – **31**. Such ligands efficiently coordinate cations of different chemical nature, including hard REE cations.[152, 177 – 180] The replacement of two carboxyl groups in acyclic EDTA with picolinate moieties [177] gives the ligand octapa (**28**) capable of forming highly stable complexes with Lu^{3+} in a serum protein medium. The complexation constants (metal complex stability constants) for picolinate ligands with REE vary in a broad range ($\log K = 8 – 20$).[175, 177, 180] The constants $\log K_{ML}$ for the picolinate-substituted bispidine ligand bispa (**29**) with La^{3+} and Lu^{3+} are 11.4 and 8.5 respectively.[175] The complexes of bispa (**29**) with Ac^{3+} and Lu^{3+} cations are stable in the presence of serum proteins. They are 10% and 30% dissociated, respectively, over 7 days. Taking into account the chemical similarity of Ac^{3+} and La^{3+} cations, it can be concluded that complexes with ligand **29** are highly stable *in vitro* despite low $\log K$.

A similar decrease in the stability constant in a series of REEs is observed for complexes with the ligand macropa (**30**): $\log K_{LaL} = 14.99$ and $\log K_{LuL} = 8.25$.[180] A larger macrocycle better coordinates cations with larger ionic radii. According to the X-ray diffraction data, the Lu^{3+} cation is displaced to one macrocyclic nitrogen atom by 0.1 Å, while La^{3+} is situated nearly in the centre of the open macrocycle

Structures 28 – 31



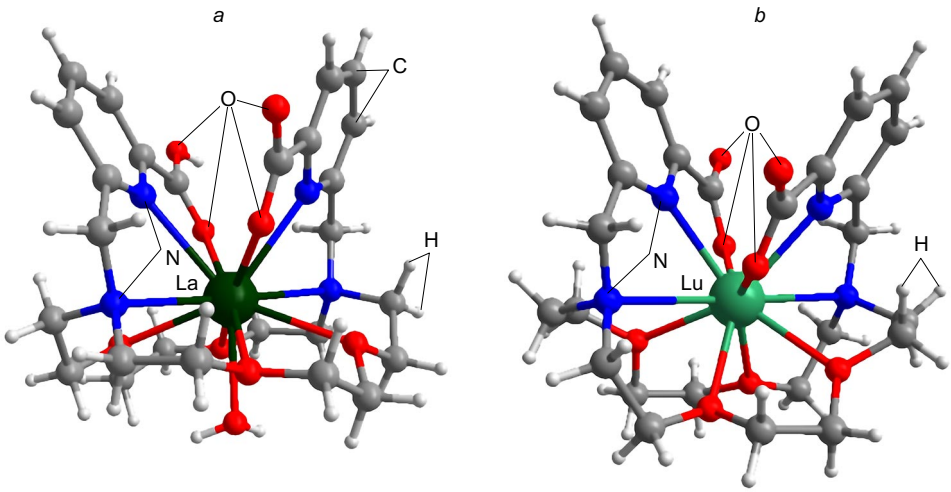


Figure 14. Molecular structures of the La-macropa (*a*) and Lu-macropa (*b*) complexes.[176]

(Fig. 14 *a*)[176] in such a way that it is coordinated by two picolinate moieties on one side and by an additional water molecule on the opposite side. In the Lu-macropa complex, the macrocycle is strongly distorted to accommodate a smaller cation, and all Lu – N and Lu – O bonds are shorter than the La – N and La – O bonds, with a similar arrangement of exocyclic groups on one side (see Fig. 14 *b*).

Taking into account high selectivity of the complexation of ligand **30** with a La^{3+} ion and the similarity of the chemical behaviour of La^{3+} and Ac^{3+}, ^{225}Ac chelates with macropa (**30**) were compared with those with DOTA (**3**).[176] The Ac-macropa complex is formed under standard conditions within a few minutes and has a specific radioactivity 100 times higher than that of the related complex with DOTA at 80 °C. Besides, this complex is characterized by *in vitro* and *in vivo* stability similar to that of the Ac-DOTA complex, resulting in rapid clearance from the body and low radioactivity uptake in the liver and spleen — the organs where free Ac^{3+} accumulates. In this case, despite a relatively low log*K*, the observed substantial *in vitro* and *in vivo* stability of Ac-macropa complexes and high complexation rate are apparently attributed to the ligand structure. The larger macrocycle size in **30** than in DOTA (**3**) makes deprotonation more rapid and enables the more rapid coordination of the cation. From this standpoint, it would be of interest to compare the Ac-macropa and Ac-HEHA complexes. However, it is impossible to properly evaluate the difference because of the different experimental conditions used in the studies.[128, 176] A labelled conjugate with a specific radioactivity of 0.6 kBq μg^{-1} was produced (99% yield) in the former study; in the latter case, the specific activity of the conjugate was 6 kBq μg^{-1} (90% yield). These conjugates exhibited different stability in the presence of serum proteins. Thus, only < 50% of Ac^{3+} remained in the Ac-HEHA-MAb complex overnight, whereas 99% of Ac^{3+} remained in the Ac-macropa-MAb complex even after 8 days.[128, 176] Apparently, the conjugation of HEHA containing a larger number of carboxyl groups to a protein molecule has an adverse impact on the complexation because it creates a certain orientation of numerous charged groups of the chelator towards regions of the protein molecule, resulting in the formation of less stable complexes in the presence of serum proteins. However, in any case, one should take into account the fact that the experiments were carried out using protein molecules with different structures.

Apart from REE complexes, ligands **31a**,**b** containing two picolinate moieties were found to be promising for the binding of Pb^{2+} and Bi^{3+} cations.[181, 182] Despite a low complexation rate of DO2PA (**31a**), the resulting complexes exhibit high stability in an acidic medium and in the presence of competing ligands. According to the X-ray diffraction data for complexes with MeDO2PA (**31b**), the picolinate moieties are coordinated on one side of the macrocycle (Fig. 15), and the cation – heteroatom bond lengths lie in a rather narrow range, the Bi – N and Bi – O

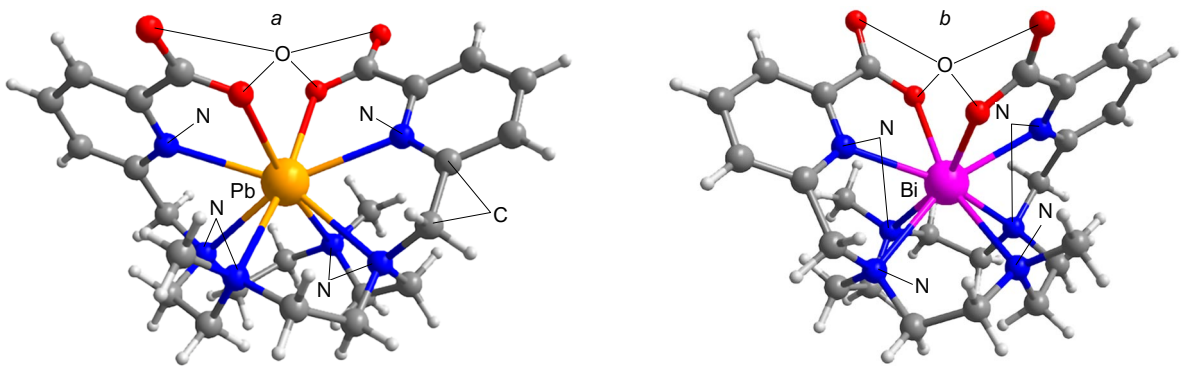


Figure 15. Molecular structures of the Pb-DO2PA (*a*) and Bi-DO2PA (*b*) complexes.[181, 182]

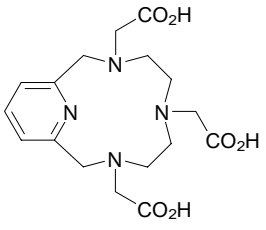
bonds (2.38–2.64 Å) being shorter than the Pb–N and Pb–O bonds (2.68–2.73 Å), which is apparently associated with the fact that Bi^{3+} is a harder Pearson cation (see Table 2).

Bifunctional derivatives of picolinate-containing ligands were synthesized and they were conjugated to monoclonal antibodies and peptides.[173, 176, 177] These conjugates were used to prepare complexes with ^{177}Lu-octapa and ^{225}Ac-macropa, which have *in vivo* stability and affinity comparable to those of conjugates with labelled DOTA (**3**). It is worth noting that the formation of these complexes does not require elevated temperatures and a long time for completion.

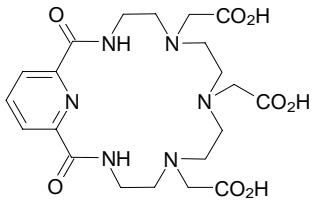
Apart from the introduction of pyridine moieties into additional chelating groups, the pyridine[183–185] and benzene[186] moieties were introduced into the macrocycle. For example, the ligand PCTA (**32**) is an analogue of DOTA (**3**). The complexation constants for **32** with cations are 3–5 orders of magnitude lower[184] ($\log K = 18–20$), but the binding rate is 10 times higher compared to compound **3**, and the complexation rate increases with decreasing size of the cation.[184] In the case of chelator **32**, pyridine is supposed to provide the preorganization of the ligand structure, which is responsible for a higher binding rate with cations compared to **3**. The binding of the cation by ligand **32** was found to occur through the formation of MH_x-PCTA intermediates. A series of bifunctional PCTA derivatives were described.[187, 188] The introduction of a bifunctional substituent was demonstrated to have almost no effect on the $\log K_{ML}$ value.[188] Pandey *et al.*[188] compared the conditions of the preparation of complexes with different specific radioactivity based on substituted PCTA and DOTA in the presence of biogenic cations. The conditions of the synthesis using PCTA (**2**) and stability of the resulting complexes were found to be similar to those of the complexes with DOTA (**3**), but high temperature is not required. Ligand **32** was used for the synthesis of ^{177}Lu-labelled RP based on MAb, which exhibited therapeutic efficacy in xenografted mice (inhibited the tumour growth).[189]

Macrocyclic ligands containing pyridine and benzene moieties[183, 185, 186] — analogues of 15-crown-5 and 18-crown-6 ethers — have high complexation rates with REE and Bi^{3+} cations, and the final complexes are stable *in vitro* and *in vivo*. It was shown that the ligand ta18c6 (**33**) is rapidly excreted from the body of healthy mice and is stable in the presence of serum proteins.[185]

Structures 32, 33



32 (PCTA)



33 (ta18c6)

4. Conclusion

The necessity and possibility of using a particular radionuclide or a combination of radionuclides for therapy of tumours of different size and localization growing at different density depend on the type and energy of radiation. Since α-particles have a short range and, as a consequence, high linear energy transfer, the possibility of using α-emitters for targeted cancer therapy has been extensively investigated in recent years. The ^{213}Bi and ^{225}Ac isotopes are currently the most studied α-particle emitters. The ^{149}Tb isotope holds promise due to a unique combination of an appropriate half-life and the presence of both β^+- and α-radiation. Moreover, ^{149}Tb, as a representative of lanthanides characterized by similar chemical, including coordination, properties, can be used with the same chelating agents and under the same conditions as for the β-emitters ^{90}Y and ^{177}Lu, which are most widely applied in the treatment of lymphoma and neuroendocrine tumours. Despite growing interest in α-emitters, the β-emitters are still the most widely used radionuclides in targeted cancer therapy. These emitters are most effective in the treatment of large or heterogeneous tumours.

However, therapeutic radiation, particularly α-radiation, is highly toxic and, consequently, the uptake of these emitters in normal cells can induce serious adverse effects. In the case of application of long-range β-emitters, there is always the possibility of damage to normal tissues, particularly bone marrow, thereby significantly impairing the hematopoietic function of the latter. At the chemical level, the problem can be diminished by preparing stable radionuclide–biological vector complexes. For this purpose, aza crowns and acyclic polyaminocarboxylates are used as chelating ligands. The currently employed ligands are characterized by either slow binding, which is critical for many short-lived medical radionuclides, or by a high dissociation rate of the complex. Thus, the rigid macrocyclic structure of DOTA (**3**) is rearranged upon complexation, which leads to an increase in the time required for binding to the cation. However, the resulting complex has high *in vivo* kinetic inertness. The acyclic ligand DTPA (**2**) is characterized by a low kinetic barrier to both the formation and dissociation of the complex. The complexation involving this ligand leads to accumulation of free cations in bones (^{90}Y, ^{177}Lu, ^{212}Pb) and kidneys (^{213}Bi), or free cations can be bound by serum proteins and circulate in the bloodstream. The chemistry of RPs is directly related to the use of trace amounts of the components. This requires that radionuclide–chelator complexes be thermodynamically stable. The stability of the resulting complex influences the specific activity of the conjugates. Thus, the cold vector that is introduced, apart from the labelled vector, in a substantial amount competes with PRs for the binding to target cells. Another important property of the chelator is its ability to form complexes with cations at room temperature, because not all biological vectors withstand the synthesis at elevated temperature.

Currently, different modifications of the ligands DTPA (**2**) and DOTA (**3**), involving the introduction of additional coordinating groups into macrocyclic and acyclic chelators, are investigated. For example, the chelators DEPA (**1**) and NETA (**17**), which are functionalized analogues of ligands **2** and **3**, respectively, more rapidly bind to radionuclides. The introduction of the rigid cyclohexyl moiety into DTPA (**24**, **25**) is used to increase kinetic stability of the complexes. Besides, different chemical properties (the ionic radius, CN, oxidation state) of cations of medical radionuclides cause the problem of selection of chelators with an appropriate combination of coordinating atoms that provides required geometric and donor characteristics. For this purpose, different derivatives and analogues of DOTA (**3**) and

DTPA (**2**) were synthesized. Therefore, DEPA (**11**), NETA (**17**), macropa (**30**) and CHX-DTPA (**24**, **25**) are currently the most promising ligands. These ligands do not require long times and high temperatures for complexation, and their complexes are stable in biological media. Interestingly, the common feature of these ligands is a combination of flexible and rigid moieties. For instance, DEPA (**11**) and NETA (**17**) contain additional aminoacetate groups, resulting in an increase in the complexation rate. In CHX-DTPA (**24**, **25**), the initially flexible acyclic ligand is partially fixed by the rigid cyclohexyl moiety. Due to a rather large macrocyclic cavity, the ligand macropa (**30**) can fold to accommodate a cation, using additional partially rigid picolinate groups for coordination. Due to the presence of an aminodiacetate group, the ligands NETA (**17**) and DEPA (**11**) can rapidly bind large cations with CN 8 – 9, including REEs and Bi^{3+}. Based on the estimation of log*K*, ligand **30** is suitable only for light lanthanides. Additional studies are required to evaluate its possible application for Bi^{3+} and Pb^{2+} cations because this ligand provides, apart from a large number of coordination sites, a space for the stereochemically active lone pair (if it is present). Taking into account that the analogue of macropa (**30**), the ligand DO2PA (**31a**) with a smaller macrocycle, is known to form complexes with Bi^{3+} and Pb^{2+} cations, an increase in the size of the macrocyclic cavity would be expected to increase the complexation rate with these cations.

It should be noted that the design of new chelators for radionuclides remains a challenge in view of the following considerations. First, there is a lack of ligands, which completely meet the requirements of the development of radiopharmaceuticals. Second, new ideas on the use of radionuclides for diagnosis and therapy are continuously arising. Recent trends, such as the inclusion of rigid moieties in acyclic ligands or an increase in flexibility of macrocyclic ligands, can give rise to a combination or properties necessary for subsequent application.

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