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Evaluation of nitrogen-rich macrocyclic ligands for the chelation of therapeutic bismuth radioisotopes

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ABSTRACT

Introduction: The use of α-emitting isotopes for radionuclide therapy is a promising treatment strategy for small micro-metastatic disease. The radioisotope ^{213}Bi is a nuclide that has found substantial use for targeted α-therapy (TAT). The relatively unexplored aqueous chemistry of Bi^{3+}, however, hinders the development of bifunctional chelating agents that can successfully deliver these Bi radioisotopes to the tumor cells. Here, a novel series of nitrogen-rich macrocyclic ligands is explored for their potential use as Bi-selective chelating agents.
Methods: The ligands, 1,4,7,10-tetrakis(pyridin-2-ylmethyl)-1,4,7,10-tetraazacyclododecane (L^{py}), 1,4,7,10-tetrakis(3-pyridazylmethyl)-1,4,7,10-tetraazacyclododecane (L^{pyd}), 1,4,7,10-tetrakis(4-pyrimidylmethyl)-1,4,7,10-tetraazacyclododecane (L^{pyr}), and 1,4,7,10-tetrakis(2-pyrazinylmethyl)-1,4,7,10-tetraazacyclododecane (L^{pz}), were prepared by a previously reported method and investigated here for their abilities to bind Bi radioisotopes. The commercially available and commonly used ligands 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and *N*-[(*R*)-2-amino-3-(*p*-isothiocyanato-phenyl)propyl]-*trans*-(*S*,*S*)- cyclohexane-1,2-diamine-*N*,*N*′,*N*″,*N*‴-pentaacetic acid (CHX-A″-DTPA) were also explored for comparative purposes. Radio-thin-layer chromatography (TLC) was used to measure the binding kinetics and stabilities of the complexes formed. The long-lived isotope, ^{207}Bi ($t_{1/2}$ = 32 years), was used for these studies. Density functional theory (DFT) calculations were also employed to probe the ligand interactions with Bi^{3+} and the generator parent ion Ac^{3+}.
Results: In contrast to DOTA and CHX-A″-DTPA, these nitrogen-rich macrocycles selectively chelate Bi^{3+} in the presence of the parent isotope Ac^{3+}. Among the four tested, L^{py} was found to exhibit optimal Bi^{3+}-binding kinetics and complex stability. L^{py} complexes Bi^{3+} more rapidly than DOTA, yet the resulting complexes are of similar stability. DFT calculations corroborate the experimentally observed selectivity of these ligands for Bi^{3+} over Ac^{3+}.
Conclusion: Taken together, these data implicate L^{py} as a valuable chelating agent for the delivery of ^{213}Bi. Its selectivity for Bi^{3+} and rapid and stable labeling properties warrant further investigation and biological studies.
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1. Introduction

High-energy α-particles emitted by the decay of radioactive isotopes can be harnessed with an appropriate biological targeting vector to destroy malignant cells [1–3]. This therapeutic strategy, known as α-therapy, is the subject of intense current research, with its utility emphasized by the recent FDA-approval of the α-emitter $^{223}RaCl_2$ for the treatment of bone metastases arising from castration-resistant prostate cancer [4]. The short range (several cell diameters) and high linear energy transfer (≈100 keV/μm) of emitted α-particles suggests their use in the treatment of micro-metastatic disease, where irradiation can be limited to the targeted cells. However, the limited availability of α-emitting nuclides with appropriate physical properties for therapy hinders their development for clinical application [5,6].

Among the radionuclides proposed for targeted α-therapy (TAT), the decay chain of ^{213}Bi ($t_{1/2}$ = 45.6 m, 97.8% β^-, 2.2% α), which entails an α emission from either of two possible branches thanks to its α-emitting daughter ^{213}Po ($t_{1/2}$ = 3.72 μs, 100% α), has shown significant promise. The short half-life of ^{213}Bi is suitable for use with small-molecule and peptide-based targeting agents. Furthermore, its short half-life and small decay chain (Fig. 1) minimize toxic side effects that may arise from long-lived daughter nuclides, which can redistribute to non-target sites in vivo [7]. ^{213}Bi can also be conveniently obtained from a generator system comprised of its longer-lived parent ^{225}Ac ($t_{1/2}$ = 9.9 d, 100% α), which is attractive for clinical use [8–11]. Such generator systems are currently commercially available from Oak Ridge National Laboratory in the United States and the Institute for Transuranium Elements in Germany, with future commercial development underway at the Institute for Physics and Power Engineering in Russia [12]. Although the widespread availability of the ^{225}Ac parent isotope is limited currently, impeding the further development of ^{213}Bi pharmaceuticals [13], significant progress has been made toward the large-scale production of ^{225}Ac [14–17]. The great therapeutic utility of ^{213}Bi is reflected by the several clinical trials that have employed this isotope for cancer treatment [18–23]. The potential of ^{213}Bi and other α-

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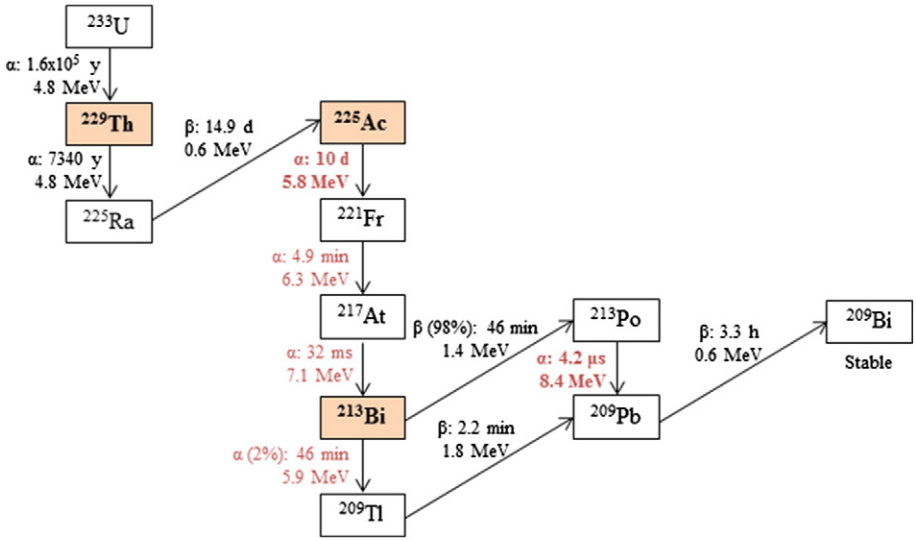

Fig. 1. Decay chain of ^{213}Bi, including ancestral isotopes from the ^{233}U decay series.

emitters for the treatment of infectious diseases is currently under intense investigation as well [24–26].

Despite the promise of ^{213}Bi TAT, the element bismuth has complicated aqueous chemistry, rendering its complexation for biological delivery challenging. The high affinity of Bi^{3+} for OH^- ($\log K = 12.9$) [27] indicates the strong tendency of this ion to hydrolyze at even at slightly acidic pH values. Challenges associated with the aqueous chemistry of Bi^{3+} have largely hindered the development and rational design of chelating ligands. Ligands currently used for TAT with ^{213}Bi are DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and CHX-A′′-DTPA (*N*-[(*R*)-2-amino-3-(*p*-isothiocyanato-phenyl)propyl]-*trans*-(*S*,*S*)-cyclohexane-1,2-diamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetic acid), shown in Fig. 2. Radiolabeling kinetics for DOTA are generally slow, and both CHX-A′′-DTPA and DOTA have high affinity for metal ions other than Bi^{3+}. The development of other bifunctional chelating agents for Bi^{3+}, which exhibit fast radiolabeling kinetics, high stability, and good metal ion selectivity, would be welcome additions to DOTA and CHX-A′′-DTPA for ^{213}Bi TAT. A ligand that is highly selective for Bi^{3+} may minimize the effects of ^{225}Ac breakthrough from the ^{225}Ac/^{213}Bi generator, which may occur after operator error.

Recently, we described a series of nitrogen-rich macrocyclic ligands and explored their coordination chemistry with La^{3+} [28]. These ligands (Fig. 2), L^{py} (1,4,7,10-tetrakis(pyridin-2-ylmethyl)-1,4,7,10-tetraazacyclododecane), L^{pyd} (1,4,7,10-tetrakis(3-pyridazylmethyl)-1,4,7,10-tetraazacyclododecane), L^{pyr} (1,4,7,10-tetrakis(4-pyrimidylmethyl)-1,4,7,10-tetraazacyclododecane), and L^{pz} (1,4,7,10-tetrakis(2-pyrazinyl methyl)-1,4,7,10-tetraazacyclododecane), are structurally homologous, varying only in the nature of the pendant *N*-heterocyclic donors. The pendant donors vary in their relative basicity and chemical hardness values. In our previous work, we demonstrated how these subtle electronic modifications across this series of ligands have significant effects on the solution behavior of their La^{3+} complexes [28]. Here, we describe the utility of this class of ligands for the selective and stable chelation of radiobismuth. The fast radiolabeling kinetics, high stability, and good selectivity for Bi^{3+} over the generator parent Ac^{3+} indicate that these ligands may be useful for ^{213}Bi TAT.

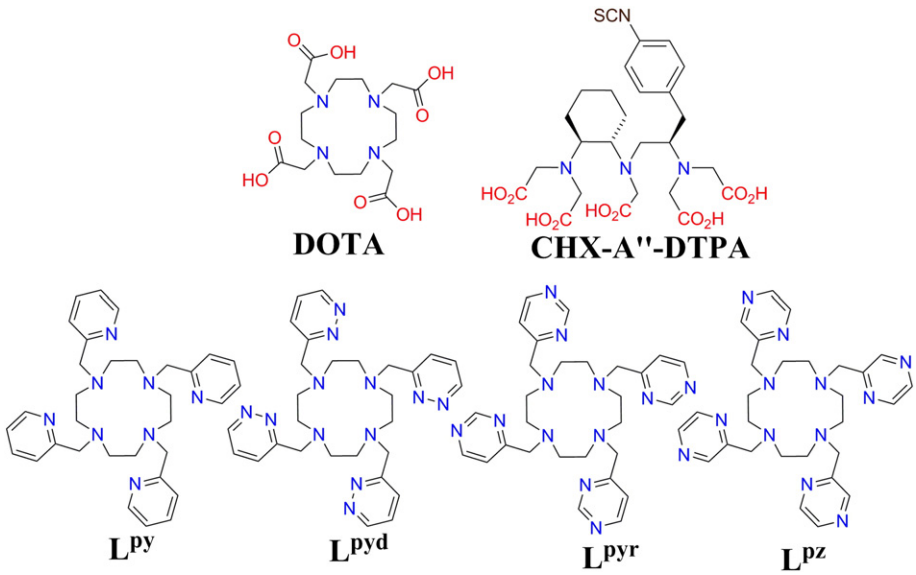

Fig. 2. Structures and abbreviated names of ligands investigated in this work.

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