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Macropa Derivatives for Radiopharmaceutical and Rare-Earth Element Separation

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Abstract

Recognition of large f-block ions underlies advances in targeted radionuclide therapy and rare-earth element separations. Like the lanthanide-binding protein lanmodulin, the 18-membered macrocycle macropa displays reverse-size selectivity characterized by its preference for binding large trivalent metal ions. Its diaza-18-crown-6 scaffold enables efficient complexation of therapeutically relevant radiometals like ^{225}Ac, ^{223}Ra, and ^{213}Bi, while accommodating diagnostic partners including ^{203}Pb and radiolanthanides. In parallel, systematic differences in stability constants across the lanthanide series enables size-based discrimination in separation chemistry. Macropa and derivatives have been deployed in different strategies to recover and purify rare-earth elements and minor actinides. This manuscript describes recent studies on modifications of macropa, including cavity expansion, alteration of donor atoms, backbone rigidification, chelator-embedded ^{18}F incorporation, and acyclic variants to demonstrate that effective selectivity arises from balancing preorganization, donor strength, and conformational adaptability. These studies establish macropa-based scaffolds as synthetic systems that bridge radiopharmaceutical coordination chemistry and rare-earth element separations.

Introduction

The discovery of lanmodulin (LanM) revealed the remarkable ability of biology to distinguish chemically similar lanthanide ions from each other, as well as from other metal ions with much higher natural abundance [1–3]. This lanthanide-binding protein exhibits a pronounced preference for the larger, early lanthanides, establishing ionic radius as a dominant determinant of selectivity across the lanthanide series, and this property has enabled its use for bio-based separations of the rare-earth elements (REEs) [4–8]. Similarly, the small-molecule synthetic macrocyclic ligand macropa also displays systematic selectivity for larger lanthanides (Figure 1) that closely parallels trends observed in LanM [9]. The preference of both LanM and macropa for the larger, early

REEs is unique, as most chelators preferably bind the more charge-dense late REEs, which engage in much stronger ionic interactions with ligand donor atoms. Structurally, LanM binds to light REEs with its four EF hand loops, affording 9- or 10-coordinate REE centers supported primarily by anionic glutamate or aspartate residues [4]. Macropa, by contrast, features an expanded 18-membered diaza-crown macrocycle appended with picolinate donors, generating a spacious yet preorganized coordination environment well matched to the large ionic radii of early lanthanides and actinides [10]. The high affinity of macropa for large metal ions has made it valuable for nuclear medicine where macropa is broadly used to efficiently coordinate α-emitting radiometals like actinium-225 (^{225}Ac), radium-223 (^{223}Ra), and bismuth-213 (^{213}Bi), as well as the large diagnostic radiometals lead-203 (^{203}Pb), lanthanum-132 (^{132}La), barium-131 (^{131}Ba), and cerium-134 (^{134}Ce) [11–24] in association with the targeting sections (antibodies or peptides) during systemic circulation, thereby minimizing metal dissociation and off-target radiation while enabling selective delivery to diseased tissue. Although LanM has been less widely explored for radiopharmaceutical purposes, it can bind the radioisotopes of lanthanum (La^{3+}), lutetium (Lu^{3+}), americium (Am^{3+}), curium (Cm^{3+}), and actinium (Ac^{3+}) [25–28]. Additionally, macropa has emerged as a powerful chelating agent for critical f-block elements, a property that was first recognized in 2014 when it was applied for solvent extraction separations of radioactive Am^{3+} and Cm^{3+} [29,30]. Subsequently, we investigated the analogue macrophosphi, where the picolinate groups of macropa are replaced by pyridyl-2-phosphinic acid arms [31], to achieve an efficient separation of the adjacent La^{3+} and Ce^{3+} ions. Collectively, these studies have established macropa to be a valuable reverse-size selective synthetic chelator with many applications in theranostic nuclear medicine and critical rare-earth element separations.

Building on the success of macropa for these applications, numerous derivatives of this chelator have been developed to further tune its metal ion affinity, selectivity, and binding kinetics. In this review, we summarize the latest studies of macropa analogues for nuclear medicine and critical REE separation applications (Figure 1). The following narrative underscores how the design and chemical structures of these macrocyclic chelators influence their coordination chemistry for metal ions and subsequently enable their applications in both fields via rational strategies.

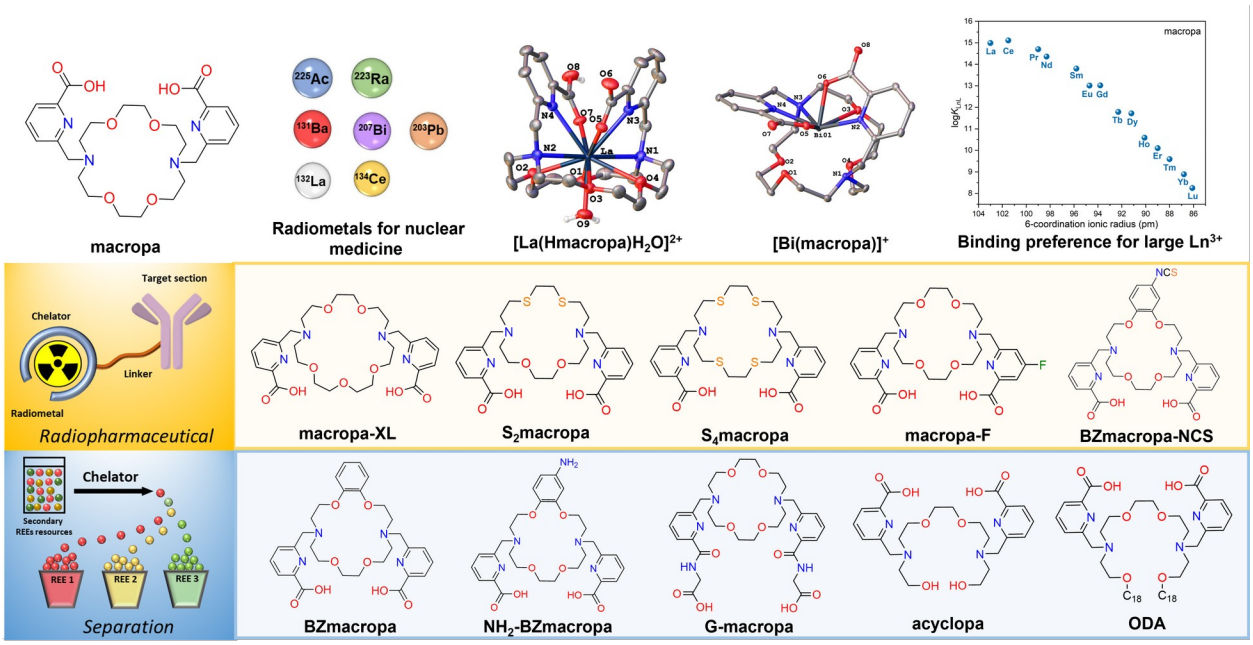

Figure 1. Macropa and its derivatives used for radiopharmaceutical and separation applications

Radiopharmaceutical Applications

Expanding the Macrocyclic Cavity for Radium-223 Chelation

^{223}Ra targeted α therapy (TAT) requires highly stable chelators to incorporate into targeting vectors and delivery to disease sites. The chelation of [^{223}Ra]Ra^{2+}, however, remains one of the most persistent challenges due to the large ionic radius (8-coordinate ionic radius = 1.48 Å) and low charge density of Ra^{2+}, which result in weak electrostatic interactions that lead to unstable complexes under physiological conditions. To better accommodate this "extra-large" ion, an expanded macropa analogue featuring a 21-membered macrocyclic core, called macropa-XL (Figure 2a), was developed and evaluated as a next-generation [^{223}Ra]Ra^{2+} chelator [32]. Structural studies using Ba^{2+} as a non-radioactive surrogate reveal formation of a high-coordinate (11-coordinate) complex that highlights its increased conformational flexibility relative to macropa (Figure 2b). However, thermodynamic measurements demonstrate that macropa-XL binds [^{223}Ra]Ra^{2+} less strongly than macropa, a trend rationalized by density functional theory (DFT) as arising from increased strain and reduced preorganization despite favorable metal–ligand interactions. Radiolabeling and serum stability studies further indicate that macrocycle expansion alone does not guarantee improved in vivo performance for [^{223}Ra]Ra^{2+} (Figure 2c). Collectively, this work underscores that effective [^{223}Ra]Ra^{2+} chelation requires not only size matching but also careful control of ligand preorganization, and it delineates

fundamental design constraints that must be addressed to advance ^{223}Ra-based TAT beyond bone-seeking applications.

Tuning Donor Softness in the Macropa Scaffold for Pb^{2+} and Bi^{3+} Chelation

Recent work has examined whether increasing donor-atom softness within macrocyclic chelators can improve coordination to therapeutically and diagnostically relevant radioisotopes of metal ions like Pb^{2+} and Bi^{3+}, which are significantly softer than REEs and actinides [33], capitalizing on the principles of hard-soft acid-base (HSAB) theory. In the H_2S_xmacropa series (Figure 2d), progressive replacement of ether donors in the macropa backbone with thioethers was used to probe this HSAB-guided design principle. Surprisingly, sulfur incorporation led to systematically reduced thermodynamic stability and kinetic inertness of both Pb^{2+} and Bi^{3+} complexes (Figures 2e), despite computational evidence for intrinsically more favorable metal–sulfur interactions. Structural and spectroscopic data indicate that all complexes remain hemidirected due to the stereochemically active $6s^2$ lone pair, and that decreased stability primarily arises from increased macrocyclic strain imposed by the acute thioether angles (≈ 98.9°) rather than poor electronic matching. Nonetheless, partial sulfur substitution preserves efficient radiolabeling and excellent serum stability for ^{203}Pb and ^{213}Bi, illustrating that donor softness must be balanced against geometric constraints when designing chelators for heavy p-block radiometals.

Direct Fluorine-18 (^{18}F) Incorporation into the Macropa Scaffold

To improve the diagnostic potential of macropa, the widely used positron-emitting tomography (PET) nuclide ^{18}F was directly incorporated into this chelator. This strategy allows for PET imaging of the ^{18}F within macropa to mimic the pharmacokinetic behavior of their therapeutic counterparts, which bear large radiometal ions. In this approach, a picolinate arm bearing a nitro group was introduced as a reactive position that could be labeled with ^{18}F, while retaining affinity for therapeutic partner radioisotopes of Pb^{2+} and Bi^{3+} [34]. Introduction of a fluorinated picolinate donor arm to afford the chelator macropa-F (Figure 2f) did not perturb the coordination geometry, thermodynamic stability, or kinetic inertness of the resulting Pb^{2+} and Bi^{3+} complexes, which retain the characteristic hemidirected coordination imposed by the stereochemically active $6s^2$ lone pair. Radiolabeling studies with surrogate isotopes demonstrate quantitative metal incorporation under mild conditions and excellent serum stability, while lipophilicity of the complex remains largely unchanged relative to the parent macropa scaffold (Figure 2g). This work highlights chelator-embedded ^{18}F as a generalizable solution to reduce the mismatch between diagnostic and α therapeutic radiopharmaceuticals, decoupling diagnostic imaging from metal-ion substitution and expanding the design space for matched PET/α-emitter radiopharmaceuticals.

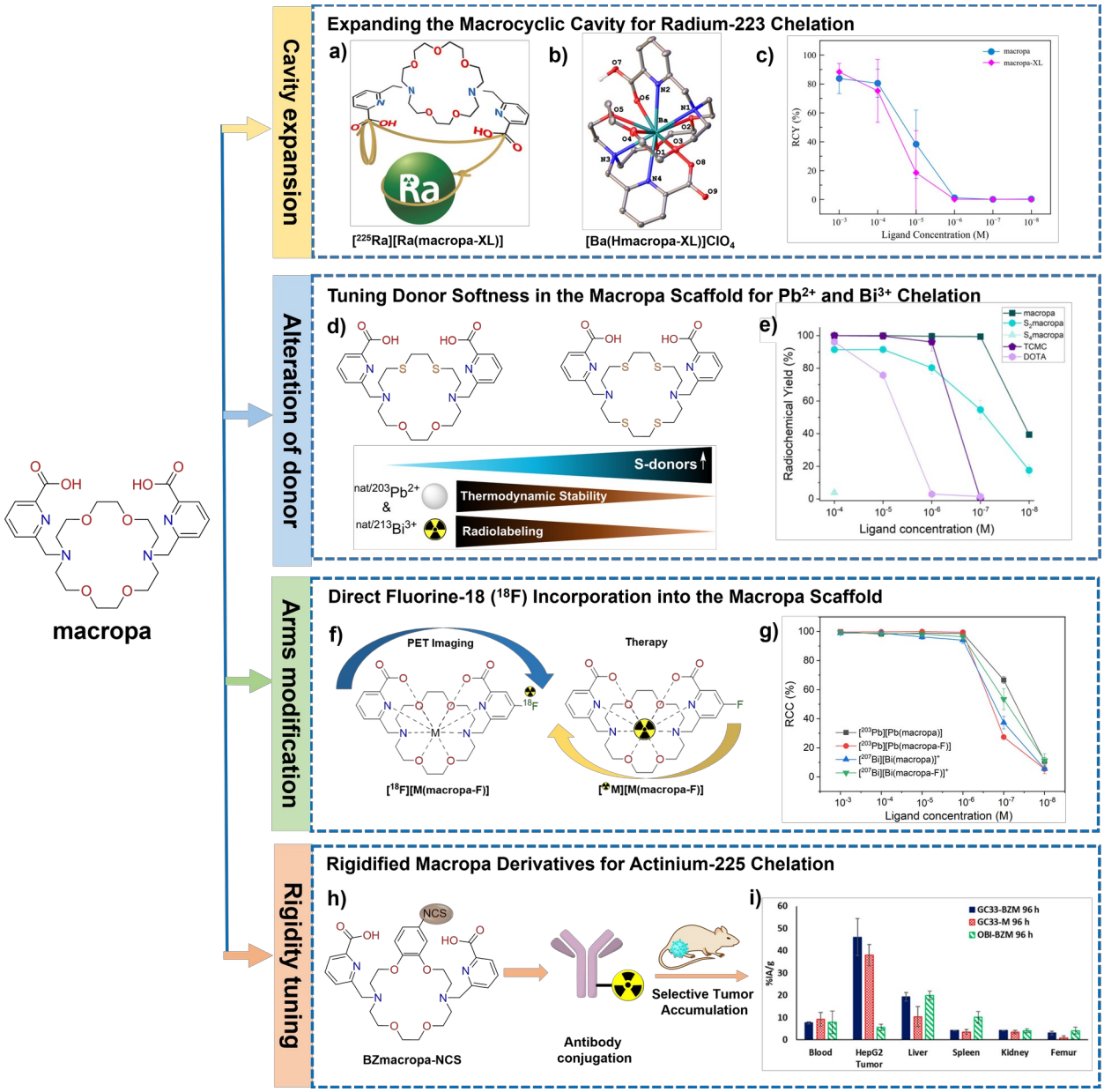

Figure 2. Depiction of the different approaches for modifying macropa. a) Macropa-XL as a novel chelator for ^{223}Ra b) X-ray crystal structure of [Ba(Hmacropa-XL)]ClO_4·2THF. c) Concentration-dependent radiolabeling of macropa-XL and macropa with ^{223}Ra (9.3 kBq). d)Thermodynamic stability and kinetic inertness trends in H_2Sxmacropa series. e) Concentration-dependent radiolabeling with [^{203}Pb]Pb^{2+}] performed in 1 M NH_4OAc buffer (pH 7). f) Imaging and therapy strategies of macropa-F. g) Concentration-dependent radiolabelling studies with different concentrations of macropa and macropa-F and ^{203}Pb or ^{207}Bi. h) Bifunctional chelator, H_2BZmacropa-NCS, was conjugated to antibody codrituzumab. i). In vivo biodistribution of ^{225}Ac-labeled chelator–antibody conjugates in HepG2 liver cancer tumor-bearing mice at 96 h. Adapted with permission from references

[32], [33], [35] (Copyright 2022 American Chemical Society) and [34] (Copyright 2024 The Royal Society of Chemistry).

Rigidified Macropa Derivatives for Actinium-225 Chelation

Building on the success of macropa as a chelator for the unusually large Ac^{3+} ion, rigidified benzene-reinforced analogues BZmacropa and BZ_2macropa (Figure 1) have been explored to probe the balance between ligand preorganization and donor strength in TAT [35]. Single-crystal X-ray diffraction of the La^{3+} complexes reveals an 11-coordinate metal center with ten macrocyclic donor atoms and an inner-sphere water molecule, closely resembling the coordination environment of the parent macropa complex. Incorporation of one or two phenyl units into the macropa backbone enhances geometric preorganization but systematically reduces thermodynamic stability with La^{3+}, a surrogate for Ac^{3+}. This trade-off is rationalized by DFT as the weaker donor strength of the phenyl ethers outweighs the reduced strain energy of the chelator. Despite this decrease in intrinsic stability inferred from the La^{3+} complex stability constants, the mono-benzene variant retains rapid, room-temperature radiolabeling with ^{225}Ac and high serum stability, motivating its development into the bifunctional chelator H_2BZmacropa-NCS (Figure 2h). Antibody conjugates of this ligand can be efficiently radiolabeled and achieve specific tumor uptake in vivo (Figure 2i), although with somewhat reduced stability and increased off-target accumulation relative to macropa-based analogues. Collectively, these results highlight that preorganization alone does not guarantee improved Ac^{3+} chelation and emphasize the need to balance macrocyclic rigidity, donor strength, and bifunctional linker effects when designing next-generation chelators for α-emitting radiometals.

Separation of Rare-Earth Elements

Immobilization on Resin for REE Separation

Inspired by the successful chemistry of BZmacropa for nuclear medicine applications, we sought to use similar conjugation chemistry to develop solid resins containing this chelator for REE extraction and separation. Toward this goal, bifunctional NH_2-BZmacropa (Figure 1) was covalently immobilized on a solid XAD-4 resin, modified to contain the electrophilic NCS group (Figure 3a) [36]. This chelator forms a complex with La^{3+} that is structurally similar to those of BZmacropa and macropa. The resulting resin could extract REEs from aqueous solution with extraction capabilities (the number of mols of REE per gram of resin) of 121.1, 68.2, and 41.2 μmol/g resin for La^{3+}, Dy^{3+}, and Lu^{3+} in a batch extraction at pH 5, respectively, demonstrating that the resin retains a preference for light REEs, like its unconjugated analogue BZmacropa. The adsorbed REEs on BZmacropa-XAD resin could be quantitively stripped with HCl, and the resin could be regenerated after neutralization with base. With this functionalized adsorbent, light La^{3+} could be separated

chromatographically from the middle Dy^{3+} and heavy Lu^{3+} by adsorption and subsequent elution with HCl at varying concentrations. Notably, BZmacropa-XAD resin could enrich the REEs in a bioleachate of electronic waste from initial molar percent of 5.2% to 57.1% (Figure 3b). These results underscore the potential of this class of chelators in solid-phase adsorbents for REE extraction and separation.

Chelator-Assisted Precipitation-Based Separation

In addition to finding use within solid resins, this class of chelators has also been investigated for its ability to modulate the selective precipitation of REEs. For example, a glycine conjugate of macropa, called G-macropa (Figure 1) [37], was applied for this application. Although G-macropa still retains a preference for light over heavy REEs, it forms REE complexes that are significantly weaker than those of macropa. Consequently, at neutral pH in aqueous solution G-macropa can only bind the light, but not heavy, REEs. With this diminished affinity, we used G-macropa to separate Nd^{3+} and Dy^{3+} via selective modulation of their precipitation with HCO_3^- (Figure 3c). In this approach, G-macropa was used to bind the light Nd^{3+} in aqueous solution, while allowing the unbound heavy Dy^{3+} to be selectively precipitated with HCO_3^- to form insoluble $Dy_2(CO_3)_2$. Under optimized conditions that use 8 equiv of G-macropa per metal ion, a very large separation factor (*SF*) of 841 could be achieved, isolating Nd^{3+} in the solution with 95% purity and Dy^{3+} in the solid with 97% purity. By contrast, macropa, which binds both metal ions more strongly than G-macropa, does not allow for any HCO_3^--mediated precipitation, leading to a failure in achieving a separation. Furthermore, this G-macropa/HCO_3^- separation approach could be used directly with NdFeB magnet waste to efficiently separate these metal ions with an *SF* of 421 (Figure 3d).

Cost-efficient Acyclic Derivatives of Macropa

For some applications, more cost-efficient chelators may be desired, especially when larger quantities are needed. Avoiding the use of the expensive diaza-18-crown-6 macrocycle, which is a precursor for macropa analogues, can lead to more cost-effective acyclic chelators. To explore this possibility, other researchers synthesized two acyclic versions of macropa, called acyclopa and octadecyl acyclopa (ODA, Figure 1) [38,39]. These variants can be viewed as “cut” versions of macropa, where the truncation points are capped by either alcohol for acyclopa or lipophilic octadecyl groups for ODA (Figure 3e). Analysis of their La^{3+} complexes via X-ray crystallography indicate that they both attain similar coordination geometries as their macropa analogues, despite the fact that they are linear chelators. Thermodynamic studies, extraction experiments, and DFT calculations show that acyclopa and ODA bind lighter Ln^{3+} ions more stably than heavier congeners, retaining the unconventional reverse-size selectivity of macropa. In addition, the lipophilic groups of ODA make it particularly useful for liquid-liquid extraction

applications. Surface-specific vibration sum-frequency generation (SFG) spectroscopy shows that the La^{3+} complex attains a pseudo-cyclic geometry at the liquid-liquid interface, facilitating phase transfer (Figure 3f). Remarkably, *SF*s of up to 6600 for La^{3+}/Tm^{3+} and 215 for Nd^{3+}/Dy^{3+} were achieved by using ODA in liquid-liquid extraction (Figure 3f), and the largest *SF* for an adjacent lanthanide pair was 4.5 for Dy^{3+}/Ho^{3+}, whereas the conventional chelators used in industries, like HDEHP, only lead to SFs of 1.5–2.0 for adjacent Ln pairs [40]. Acyclopa, on the other hand, was applied for direct dissolution-based separations of insoluble $REE(OH)_3$ mixtures. With this process, it can achieve a *SF* of 295 for the La^{3+}/Y^{3+} pair via dissolution of a mixture of their $REE(OH)_3$ solid. These results demonstrate that the unique reverse-size selectivity of macropa can be achieved via carefully designed acyclic analogues.

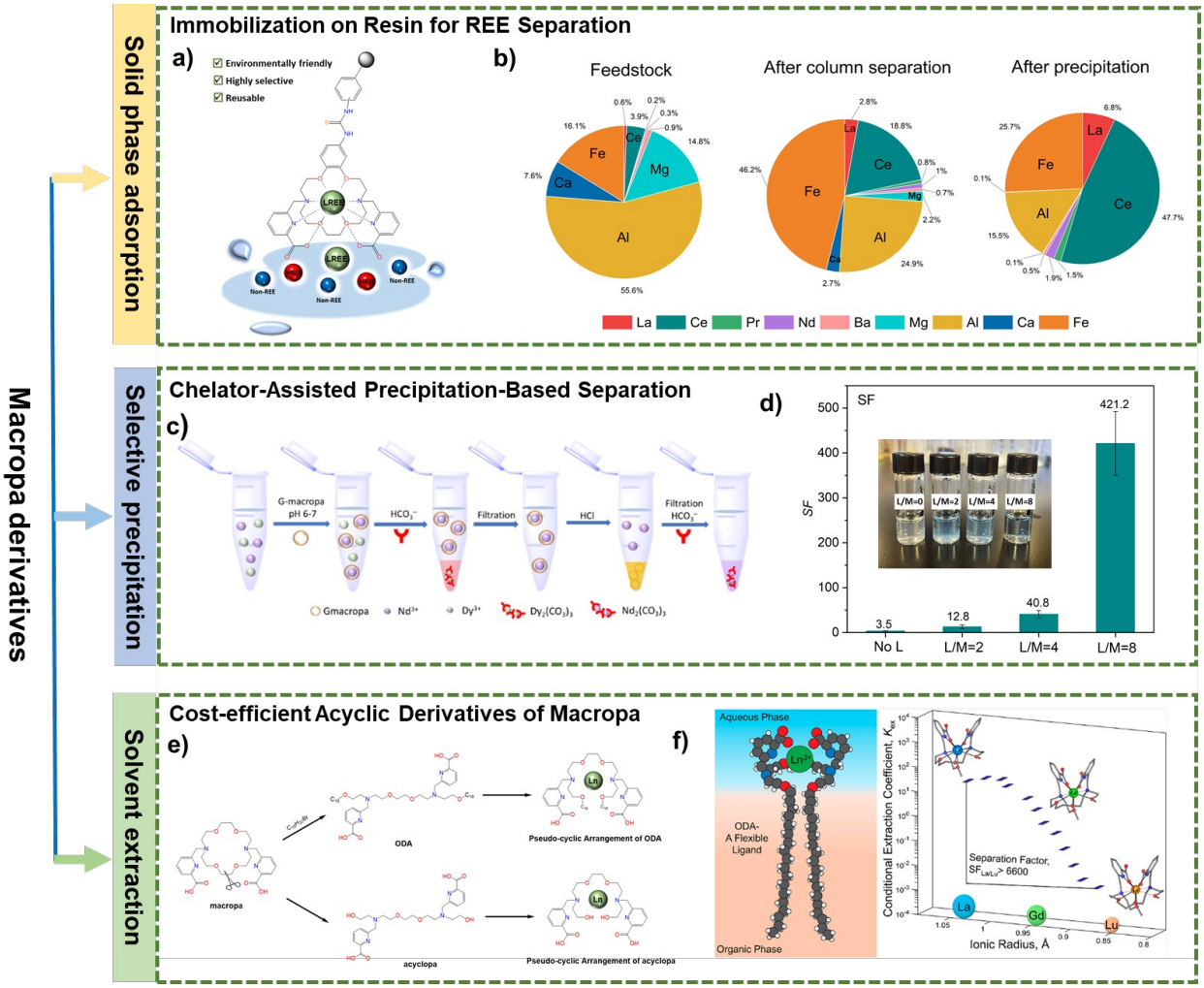

Figure 3. a) BZmacropa-XAD resin for REE extraction from electronic waste biological leachate solution. b) Metal molar percent at different processing stages of the bioleachate.

c) Depiction of the separation of Nd^{3+}/Dy^{3+} using G-macropa and HCO_3^-. d) The $SF_{Dy/Nd}$ from G-macropa/HCO_3^- precipitation of magnet leachate at different L/M ratios. e) Design of acyclopa and ODA. f). Conformation of ODA at the interface and conditional extraction coefficients, K_{ex}. Adapted with permission from references [36] (Copyright 2025 Springer Nature Limited),[37] (Copyright 2024 Wiley-VCH GmbH), and [38] (Copyright 2025 American Chemical Society).

Conclusion and Outlook

In summary, macropa and its derivatives represent a promising class of synthetic chelators that bridge fundamental coordination chemistry with practical applications in both nuclear medicine and REE separations. Their expanded macrocyclic architecture imparts predictable, size-dependent selectivity, particularly for early lanthanides, enabling translation across radiometal complexation, solvent extraction, selective precipitation, and solid-phase adsorption approaches. The complementary development of chelators like macrophospho, macroHOPO, H_2KHQ, and macroMephos [41–44], further broadens this structural family, reinforcing the importance of donor arrangement in tuning metal discrimination. Looking forward, the integration of computationally guided ligand design, as demonstrated in related crown ether systems, provides a rational pathway to refine selectivity and efficiency [45,46]. Together, these advances position macropa-inspired scaffolds as foundational tools for next-generation radiopharmaceutical chemistry and sustainable REE separation technologies.

Author Contributions

KKL, YG, and JJW conceptualized the review, performed the literature analysis, and wrote and edited the manuscript. All authors have given approval to the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Data Availability

No data was used for the research described in the article.

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** of outstanding interest

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This study systematically replaces macrocyclic ether donors in macropa with thioethers to probe HSAB effects in Pb^{2+} and Bi^{3+} coordination. Contrary to expectations, increasing sulfur content decreased thermodynamic stability and kinetic inertness due to steric strain. The work clarifies structure–stability relationships for intermediate radiometals and informs donor-atom design in theranostic chelators.

34.** Kanagasundaram T, Sun Y, Lee KK, MacMillan SN, Brugarolas P, Wilson JJ: **Fluorine-18 incorporation and radiometal coordination in macropa ligands for PET imaging and targeted alpha therapy**. *Chem Commun* 2024, **60**:11940–11943.

This work demonstrates direct backbone incorporation of ^{18}F into macropa to generate a radiofluorinated chelator that retains high-affinity for Pb^{2+} and Bi^{3+}. The resulting ^{18}F-labeled and radiometal complexes show quantitative radiolabeling and >95% serum stability, establishing a proof-of-concept strategy for matched PET/α-therapy theranostics using ^{18}F-functionalized radiometal chelators.

35. Kadassery KJ, King AP, Fayn S, Baidoo KE, MacMillan SN, Escorcia FE, Wilson JJ: **H_2BZmacropa-NCS: a bifunctional chelator for actinium-225 targeted alpha therapy**. *Bioconjugate Chem* 2022, **33**:1222–1231.

36.** Gao Y, Ivanovich K, Medin S, Pian B, MacMillan SN, Schmitz AM, Wilson JJ: **18-membered macrocycle appended on resin for selective rare earth element extraction and separation**. *Commun Chem* 2025, **8**:176.

This study reports a BZmacropa-functionalized resin that retains the reverse-size selectivity of the parent macrocycle, enabling preferential extraction of light over heavy REEs. The material achieves efficient batch and column separations, recyclability, and selective enrichment of REEs from complex slag bioleachate, demonstrating the viability of macrocycle-appended solid supports for sustainable rare-earth recovery.

37.** Gao Y, Licup GL, Bigham NP, Cantu DC, Wilson JJ: **Chelator-assisted precipitation-based separation of the rare earth elements neodymium and dysprosium from aqueous solutions**. *Angew Chem Int Ed* 2024, **63**:e202410233.

This study introduces G-macropa, a reverse-size selective macrocyclic chelator that enables an efficient, fully aqueous precipitation-based separation of Nd^{3+} and Dy^{3+}. By selectively stabilizing Nd^{3+} in solution while allowing Dy^{3+} to precipitate as $Dy_2(CO_3)_3$, the method achieves separation factors up to 841 and demonstrates ligand recyclability. This work establishes an environmentally benign alternative to conventional solvent extraction for critical rare-earth separations.

38.** Islam MF, Lin L, Ray D, Premadasa UI, Ma Y-Z, Sacci RL, Kertesz V, Custelcean R, Bryantsev VS, Doughty B, et al.: **Conformationally adaptable extractant flexes strong lanthanide reverse-size selectivity**. *J Am Chem Soc* 2025, **147**:5080–5088.

This work introduces a conformationally flexible acyclic extractant (ODA) that displays strong reverse-size selectivity, preferentially extracting light over heavy Ln^{3+} ions. Spectroscopic and computational studies reveal that collective backbone interactions and reduced conformational fluctuations for larger ions underpin the thermodynamic selectivity, establishing conformational adaptability as a new strategy for unconventional lanthanide separations.

39. Thiele N, Moyer BA, Dempsey J, inventors; UT-Battelle, LLC, assignee: **Size-selective acyclic chelators and their use for the recovery of rare earth elements** US Provisional Patent US20240294553. Filing Date, 2024 Sep 5.

40. Zhang W, Feng D, Xie X, Tong X, Du Y, Cao Y; **Solvent extraction and separation of light rare earths from chloride media using HDEHP-P350 system**. *J. Rare Earth* 2022, **40**: 328–337.

41.* Siakalli C, E. Osborne B, K. Brown R, Rocco C, Weiss D, V. García-España E, V. Grundler P, N. Moiseeva A, Talip Z, Meulen NP van der, et al.: **Hydroxyquinoline-**

functionalised aza-crown macrocycles for lanthanide coordination. *Dalton Trans* 2026, **55**:3412–3421.

This work describes a quinoline-based chelator capable of coordinating lanthanide ions such as La^{3+} and Tb^{3+}. Structural studies revealed a 10-coordinate La^{3+} complex, and radiolabeling experiments achieved ~92% incorporation of ^{161}Tb under mild conditions, demonstrating potential for terbium-based theranostic radiopharmaceutical development.

42.* Franchi S, Madabeni A, Tosato M, Gentile S, Asti M, Orian L, Di Marco V: **Navigating through the coordination preferences of heavy alkaline earth metals: Laying the foundations for ^{223}Ra- and ^{131}/^{135m}Ba-based targeted alpha therapy and theranostics of cancer**. *J Inorg Biochem* 2024, **256**:112569.

This work systematically examines the coordination preferences of Ra^{2+} and Ba^{2+} using DFT calculations and experimental stability measurements. The study identifies negatively charged oxygen-donor ligands—particularly picolinate, malonate, and hydroxypyridone—as the most promising motifs for designing chelators capable of stabilizing these heavy alkaline-earth radiometals for TAT and theranostic applications.

43.* Franchi S, Asti M, Blei MK, Pozzo S, Madabeni A, Graiff C, Menegazzo I, Volpato F, Gentile S, Orian L, et al.: **Heavy alkaline earth radiometals for cancer theranostics: coordination and radiochemistry of radium-223 and barium-131 with kryptofix 22-based chelators**. *Inorg Chem* 2025, **64**:22422–22440.

This work examines the coordination chemistry of Ra^{2+} and Ba^{2+} using a series of Kryptofix-22-derived macrocyclic chelators. Thermodynamic, spectroscopic, and computational studies show that a malonate-functionalized ligand provides the highest Ba^{2+} stability ($\log K = 16.6$), exceeding macropa. Radiolabeling studies with ^{223}Ra and ^{131}Ba highlight ongoing challenges in stabilizing heavy alkaline-earth radiometals while advancing ligand design for Ra-based targeted α-therapy and theranostic imaging.

44.* Southwell JW, Gumiela M, Cowell J, Brandt MR, Tekin V, Sterba JH, Rosecker V, Mindt TL, Gasser G: **Synthesis, Characterization, and Evaluation of Chelators for Radium-223**. *Inorg Chem* 2026, doi:10.1021/acs.inorgchem.5c04877.

This study reports the synthesis of novel chelators designed to bind the large Ra^{2+} ion for potential targeted alpha therapy with radium-223. The ligands were characterized using spectroscopic and structural methods and evaluated through thermodynamic and radiolabeling studies. 14 of 17 chelators achieved quantitive radiolabeling yield, demonstrating varying stability and providing insights into ligand design for effective radium chelation.

45.* Summers TJ, Taylor MG, Augustine LJ, Janssen J, Perez D, Batista ER, Yang P: **On the importance of configuration search to the predictivity of lanthanide selectivity**. *JACS Au* 2025, **5**:631–641.

This work introduces a high-throughput computational workflow that combines automated structure generation and DFT calculations to predict lanthanide extraction selectivity. The study shows that thorough configurational sampling of metal–ligand complexes is essential for correctly predicting lanthanide selectivity trends, highlighting the importance of automated structure searches in computational screening of extractants.

46.* Zhang B, Summers TJ, Augustine LJ, Taylor MG, Geist A, Li R, Batista ER, Perez D, Yang P, Schrier J: **Augmenting large language models for automated discovery of f-element extractants**. *J Am Chem Soc* 2026, **148**:5520–5532.

This study introduces SAFE-MolGen, an AI-driven workflow that combines large language models, machine learning, and DFT calculations to design extractant ligands for f-element separations. Application to Am(III)/Eu(III) separation generated over 1000 candidate molecules and identified several predicted to outperform the benchmark extractant $CyMe_4BTBP$, highlighting the potential of AI-assisted ligand discovery for actinide–lanthanide separations.