

Harnessing the Coordination Chemistry of 1,4,7-Triazacyclononane for Biomimicry and Radiopharmaceutical Applications

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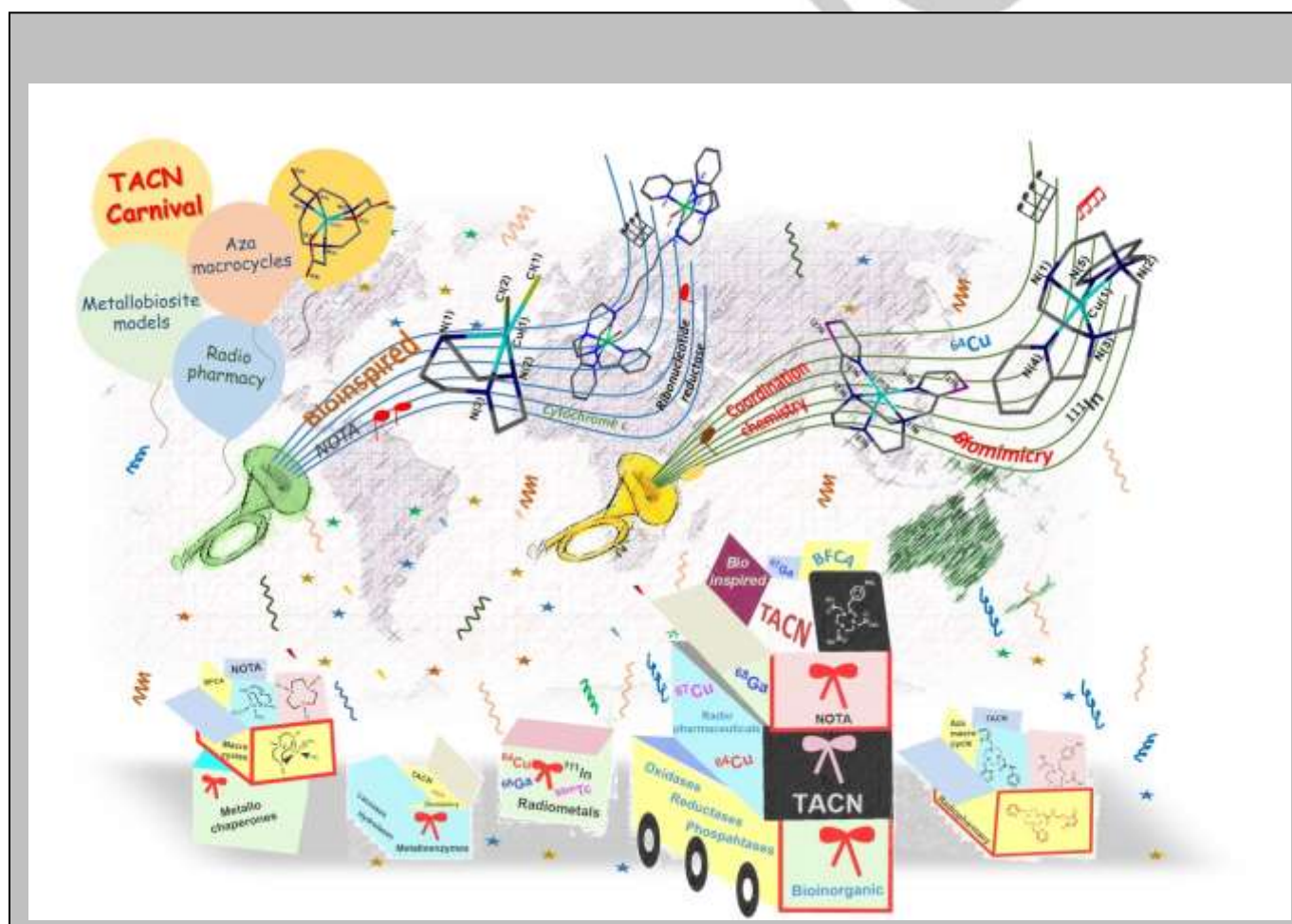
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Harnessing the Coordination Chemistry of 1,4,7-Triazacyclononane for Biomimicry and Radiopharmaceutical Applications

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In memory of Leone Spiccia



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Abstract: TACN-based mono- and poly-nuclear metal complexes have found extensive use as biological mimics for understanding the structural and operational aspects of complex natural systems. Their coordination flexibility has also provided researchers access to a vast library of radiometal binding motifs that display excellent thermodynamic stability and kinetic inertness upon metal complexation. Synthetic modification on the TACN backbone has yielded ligands that can form metal complexes with coordination geometries well-suited for these applications. In particular, Leone Spiccia's research has played a significant role in accelerating the progress in these two fields. With a focus on providing an overview of his contributions to the biomimicry and radiopharmaceutical disciplines, this minireview uses relevant examples to put in perspective the utility of macrocyclic coordination chemistry for biological inorganic chemistry applications.

Introduction

Macrocyclic motifs, specifically metal complexes of azamacrocyclic ligands, present a powerful toolkit for tackling some key challenges in biological inorganic chemistry research.^[1-14] Critical for these applications is to exploit the basic principles of coordination chemistry, including Pearson's "hard and soft acids and bases" (HSAB) theory, coordination geometry preferences, and the thermodynamic stability and kinetic inertness of metal complexes.^[1,3,5-7,10,12-13,15-17] 1,4,7-Triazacyclononane ([9]aneN₃ or TACN, Scheme 1) derivatives represent particularly attractive candidates in this regard since, compared to other tri- or tetradentate chelating ligands, their metal complexes can have much larger stability constants.^[1,18] Synthetic elaboration of TACN with a range of pendant groups has proven successful for controlling the coordination sphere and manipulating the metal complexation ability, as well as for introducing imaging and sensing capabilities.^[8-9,11,13,17-18] Research has generated structural and functional models for active sites of a number of metalloenzymes,^[2-3,9,11-12,18] which have deeply contributed to our understanding of different aspects of these natural systems. Similarly, a number of symmetrical and unsymmetrical TACN-derivatives integrated with chemically accessible side-arms have been generated for various medicinal chemistry applications.^[7-9,11-12,18] In this minireview, we bring together some of the examples that illustrate the utility of TACN-based scaffolds for developing effective chelators for radiopharmaceutical applications as well as bioinspired small molecule mimics. In particular, the aim of this review is to highlight some of the relevant structural and

functional models prepared by the group of Leone Spiccia. As emphasised herein, this work has played an instrumental role in advancing our understanding of the coordinative interactions which are essential for strong metal ion-ligation in a complex biological setting, including the microenvironment of natural systems.

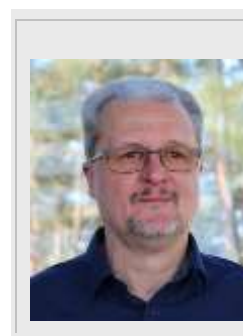
Tanmaya Joshi pursued his PhD (2008–2012) at Monash University under the supervision of Prof. Leone Spiccia. After his first postdoc with Gilles Gasser (University of Zurich), he made a move back to Australia to join the "Spicciaion Clan" as a senior postdoc (2013–2016). Since Nov 2016, he is a Humboldt Fellow at the Institute of Radiopharmaceutical Cancer Research, Helmholtz-Zentrum Dresden-Rossendorf. His current research focus is on combined application of coordination chemistry and nanomaterials for the development of new imaging, therapeutic and diagnostic agents.



Gilles Gasser undertook a PhD with Helen Stoeckli-Evans (University of Neuchâtel, Switzerland) and two post-docs with Profs. Leone Spiccia (Monash University, Australia) and Nils Metzler Nolte (Ruhr-University Bochum, Germany). Gilles took his first independent scientific position at the University of Zurich in 2010. In 2016, Gilles moved to Chimie ParisTech, PSL University (France). Gilles was the recipient of several fellowships and awards including the Alfred Werner Award, an ERC Consolidator Grant, the Jucker Award and recently the EuroBIC Medal Award.



Holger Stephan studied chemistry and received his PhD degree from the Bergakademie Freiberg in 1989. Then, Holger moved to the TU Dresden and worked with Prof. Karsten Gloe in the field of Supramolecular Chemistry. He is currently leading the "Nanoscale Systems" group at the Institute of Radiopharmaceutical Cancer Research of the Helmholtz-Zentrum Dresden-Rossendorf. His research focuses on the development of radiometal complexes, including functionalised nanoparticles for therapeutic and diagnostic applications, where he collaborated with Leone Spiccia for 10 years.



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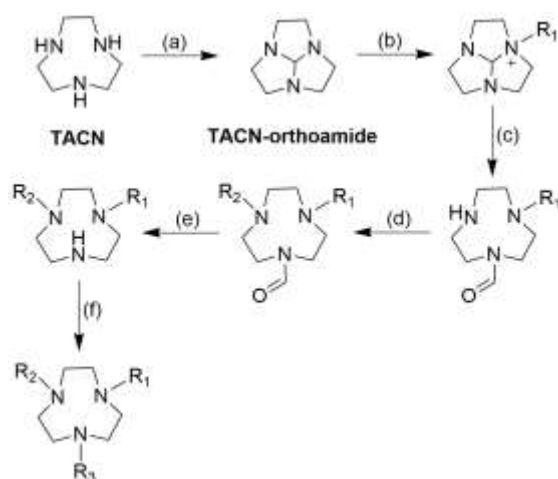
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Structural models for metallobiosites

Synthetic considerations

Much of the work in designing TACN-based models for active sites of metalloenzymes has involved the development of

synthetic routes to access suitably functionalised macrocycles as well as assemblies containing multiple linked macrocyclic units. "TACN-orthoamide" (Scheme 1), first reported by Atkins,^[19] has proven to be a very versatile synthon in this regard.^[20] It can be used to access ligands containing a variety of pendant groups, such as coordinating alcohol, amine, carboxylate and pyridyl groups, as well as non-coordinating aliphatic and aromatic groups (Scheme 1).^[18,21] TACN-orthoamide is highly reactive towards a variety of electrophiles,^[20] forming an amidinium salt, which can be easily hydrolysed in aqueous solution to yield a formyl derivative. This, in turn, can be reacted with a second electrophile and, following acidic hydrolysis of the resulting intermediate, with a third electrophile to form a trisubstituted, asymmetric TACN derivative, $R_1R_2R_3$ TACN. Other derivatives of type $(R_1)_2R_2$ TACN or $(R_1)_2$ TACN can be produced by firstly hydrolysing TACN-orthoamide to the formyl derivative and then repeating steps (d) to (f), or terminating at step (e).^[18]



Scheme 1. Synthesis of functionalised TACN-based ligands. Reagents and conditions: (a) dimethylformamide dimethylacetal, CH_3CN , 85°C , $0/n$; (b) $\text{R}_1\text{-Br}/\text{I}$, CH_3CN , rt, 18 h; (c) H_2O , reflux, 4 h; (d) $\text{R}_2\text{-Br}/\text{I}$, CH_3CN , Na_2CO_3 , reflux, 3 d; (e) 5 M HCl , reflux, 8 h; (f) $\text{R}_3\text{-Br}/\text{I}$, CH_3CN , Na_2CO_3 , reflux, 3 d.

For the synthesis of multi-TACN ligand assemblies (Figure 1),^[18] the orthoamide is first reacted with various bis/tris/tetrakis-electrophiles to generate poly-amidinium salts; these are then hydrolysed to yield the final products. There is also a possibility to introduce additional substituents onto the linked TACN rings, both following the initial aqueous hydrolysis of the poly-amidinium salts, and/or after the acidic hydrolysis step. Because of its simplicity and versatility, the TACN-orthoamide approach to substituted and/or polymacrocyclic TACN systems has largely superseded older routes based on the use of tosylate precursors or diprotected TACN derivatives.^[18,21-23]

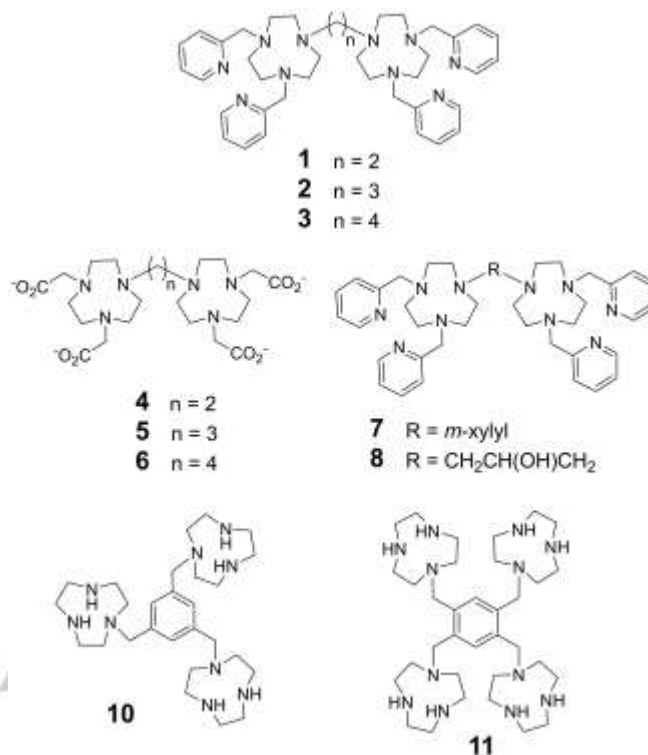


Figure 1. Examples of multi-TACN ligands developed by Spiccia and co-workers.^[18]

Metallobiosite mimicry

TACN has been extensively used to create viable models of copper protein active sites.^[2,10,12,18] For example, Cu-TACN complexes have been employed in the development of simplified models for the mono-, di- or trinuclear Cu-ligating environment found in catechol oxidase, cytochrome c oxidase, nitrite reductase, galactose oxidase, laccase, ceruloplasmin, and dicopper dismutase.^[2,8-9,11-12,18,24] Examination of the X-ray structures of a large number of copper proteins has revealed that, in most cases, the Cu(II) centre resides in a square pyramidal (SP) coordination environment generated from the histidine residues present within the protein and the aqua ligands.^[8-9,24] Structural studies on bis(TACN)-based synthetic multinuclear Cu(II) complexes (e.g., Cu(II)-**1–8**) also established a similar SP geometry about the Cu(II) centre.^[18] The stabilisation of this geometry over a trigonal pyramidal one lends support to the contention that the TACN prefers to occupy one of the four smaller faces of an axially elongated square pyramid than the larger face of a trigonal pyramid.^[1] Systematic variation of the intramolecular Cu...Cu distance in these binuclear models also showed that the electronic interaction between the Cu(II) centres diminishes with increasing separation. The complexes studied range from ones that display moderate antiferromagnetic coupling, e.g., Cu(II)₂-**12** ($J = -86 \text{ cm}^{-1}$),^[25] featuring an endogenous alkoxo-bridged pair of Cu(II) centres separated by $\sim 3.6 \text{ \AA}$, through to ones exhibiting strong antiferromagnetic interaction between the Cu(II) centres, e.g., Cu(II)₂-**13** ($J \approx -150$

cm^{-1}),^[26] an oxalato-bridged binuclear Cu(II) complex with a very large Cu...Cu separation ($\sim 5.2 \text{ \AA}$) (Figure 2).

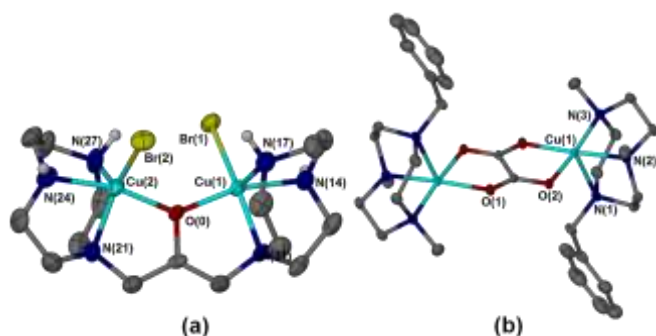


Figure 2. X-ray crystal structures of (a) Cu(II)₂-12 and (b) Cu(II)₂-13. Adapted with permission from refs. 25-26. Copyright 2003 Royal Society of Chemistry and 2006 John Wiley and Sons.

This distance is further reduced ($\sim 3.80 \text{ \AA}$) in Cu(II)₂-14, a *cis*-Cu^I₂(μ - η^1 : η^1 -O₂) complex of pyrazole-bridged TACN (Figure 3), reported by Meyer and co-workers.^[8] This particular complex illustrates one of the ways in which the copper proteins may activate dioxygen.^[2,8]

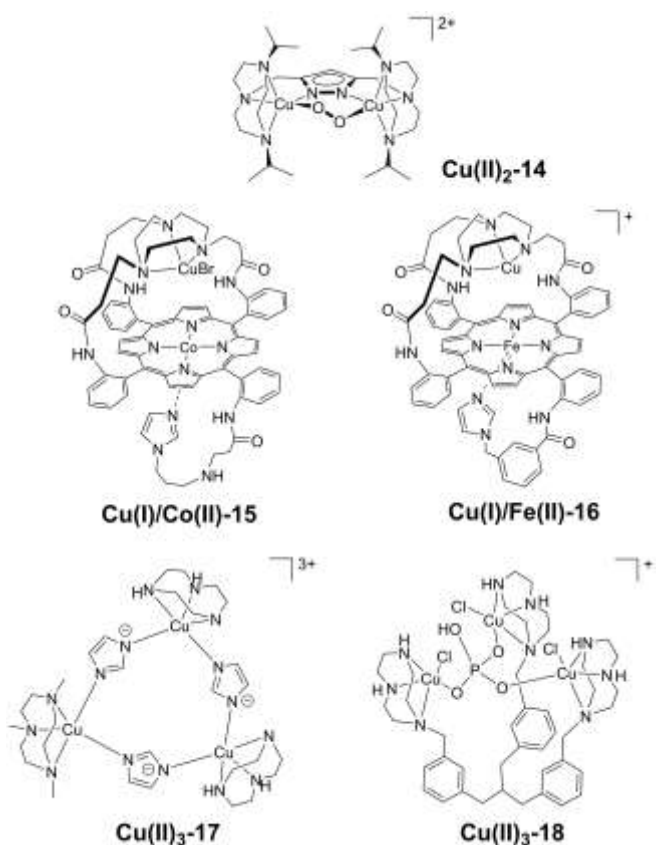


Figure 3. Examples of multinuclear Cu(II) complexes applied in biomimicry.^[8,16,27-28]

Cu(I)-TACN complexes have also shown ability to catalyse dioxygen reduction to H₂O, akin to cytochrome c oxidase.^[2,16,27] For instance, heterobimetallic Cu(I)/M(II) (M=Co, Fe) complexes,

Cu(I)/Co(II)-15 and Cu(I)/Fe(II)-16, developed by Collman et al. could electrocatalytically effect the 4e⁻ reduction of O₂ to H₂O at physiological pH, with little to no peroxide release (Figure 3).^[16,27]

Imidazolate-bridged Cu(II)₃-17 (Figure 3) is another complex that structurally mimics the trinuclear unit of the natural ascorbate oxidase (AO).^[28] X-ray structure of this Cu₃ adduct revealed a Cu...Cu separation of 5.92 Å. In addition, the complex exhibits spin-frustration due to the three Cu(II) centres being equivalent to each other. In comparison to the intermetallic separations (3.4, 3.9, and 4.0 Å) in the AO active site, the metal centres in Cu(II)₃-17 lie further apart because the Cu(II)-TACN units are interconnected via imidazolate instead of a μ ₃-X coordinating ligand.^[28] A unique trimetallic cluster modelling the active site of phosphate-metabolising enzymes was reported by Lippard and co-workers (Cu(II)₃-18, Figure 3).^[29] Reacting 18, a tripodal tris(TACN) ligand, with CuCl₂ in the presence of HPO₄²⁻ yielded a phosphate-bridged tricopper assembly that not only remained intact upon dissolution, but also demonstrated efficient phosphoester hydrolysis.^[29]

Nickel is present at the active sites of enzymes such as carbon monoxide dehydrogenase, urease and [Ni-Fe]-hydrogenase, while manganese-containing active sites are present in biological systems such as photosystem II, ribonucleotide reductase, superoxide dismutase and Mn catalases.^[6,9-10,30-32] Likewise, Zn(II) is present at the active sites of enzymes responsible for catalysing hydration reactions, RNA polymerization or phosphoryl transfer reactions, and μ -oxo/hydroxo-diiron motifs are present in non-haeme, non-sulfur iron proteins carrying out specific functions such as dioxygen transport and storage (haemerythrin), alkane hydroxylation (methane monooxygenase), and phosphate ester hydrolysis (purple acid phosphatases).^[6,10,14,33-35] This has sparked interest in the development of TACN-based (polynuclear) Mn(II), Ni(II), Zn(II) and Fe(III) complexes as synthetic mimics. For example, pentadentate TACN rings when linked by an endogenous 2-propanol-based alkoxy bridge produced a binuclear Zn(II) complex, Zn(II)₂-8 (Figure 4) with Zn...Zn separation very similar to the dizinc active site of alkaline phosphatase (3.94 Å).^[22] Interestingly, the M...M distances in related binuclear Zn(II)- and Ni(II)-TACN complexes devoid of the 2-pyridyl pendant were significantly shorter (3.68 and 3.81 Å, respectively).^[25,36]

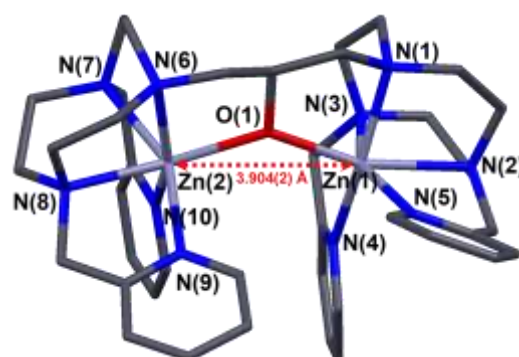


Figure 4. X-ray crystal structure of Zn(II)₂-8. Adapted with permission from ref 25. Copyright 2003 Royal Society of Chemistry.

Electrochemical measurements on binuclear Mn(II) and Ni(II) complexes of bis(pentadentate) TACN (e.g., **1–8** in Figure 1) have established that, in general, the oxidation potential for the individual metal centres decreases with an increase in the M...M separation.^[36–39] These distances were found to be shorter in the Mn(II) complexes than those in the corresponding Ni(II) complexes, viz. 8.279(3) Å vs. 9.563(4) Å for the butyl-bridged complexes, Mn(II)₂-**3** and Ni(II)₂-**3**, respectively.^[39–40] This may have its origin in the differing coordination geometries, i.e., distorted octahedral for the Ni(II) centres, vs. intermediate between octahedral and trigonal prismatic for the Mn(II) centres (Figure 5).^[39–40]

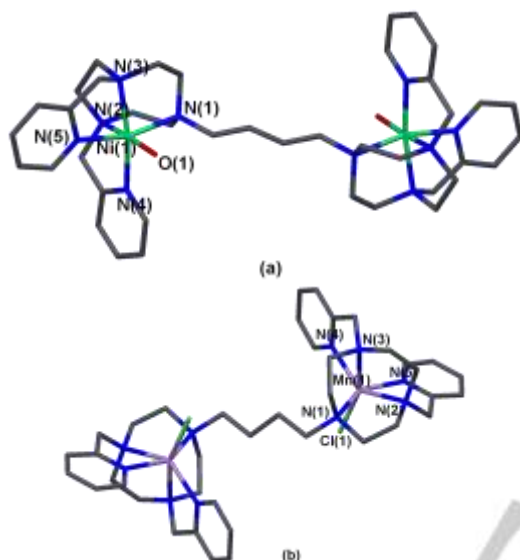


Figure 5. X-ray crystal structures of (a) Ni(II)₂-**3**, and (b) Mn(II)₂-**3**. Adapted with permission from refs. 39–40. Copyright 2000 American Chemical Society.

An oxo-bridged diiron(III) complex, Fe(III)₂-**19** (Figure 6), incorporating a bridging carboxylate, was proposed to be a good model for haemerythrin and ribonucleotide reductase B2, as the Fe...Fe separation of 3.21 Å matched closely those for the diiron(III) sites in these metalloproteins (Figure 6).^[41] Additionally, several other bioinspired models for active bimetallic sites in metalloproteins have also been developed (representative examples are shown in Figure 7).^[2,5,8–9,16,18,42–45] Taken together, the above examples clearly demonstrate the versatility of TACN-based ligands in the construction of simple bimetallic as well as higher nuclearity systems that are able to broadly mimic the structural and, in some cases, spectral and magnetic features of the active sites of several important metalloenzymes.

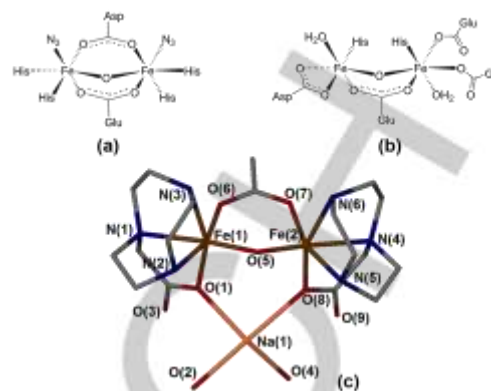


Figure 6. Active sites of (a) met-azido-haemerythrin and (b) B2 subunit of ribonucleotide reductase, and (c) the X-ray crystal structure of Fe(III)₂-**19**. Adapted with permission from ref 41. Copyright 1997 Royal Society of Chemistry.

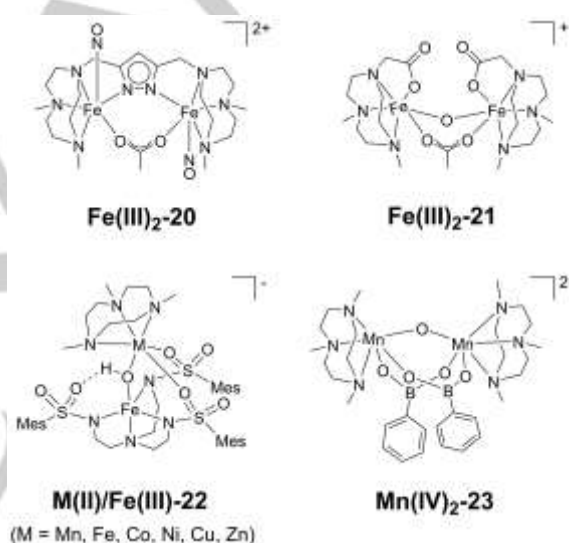


Figure 7. Other examples of non-copper containing bimetallic metallobiosite models.^[42–45]

Radiopharmaceutical Chelates

TACN-based radiocopper chelators

A variety of TACN motifs bearing pendant amine, amide, sulfhydryl, carboxyl, phosphinate, phosphonate, imidazolyl, thiazolyl, pyridinyl and pyrazolyl groups have been investigated as azamacrocyclic chelators for radiometals (Figure 8).^[46–54] Examples of such radiometals include the imaging-related gamma- and positron-emitting radioisotopes ⁶⁷Ga, ^{99m}Tc, ¹¹¹In, ¹⁷⁷Lu for single photon emission computed tomography (SPECT), ⁶⁸Ga, ⁶⁴Cu, ⁴⁴Sc, ⁸⁶Y for positron emission tomography (PET) as well as particle-emitting (beta and alpha) ⁴⁷Sc, ⁹⁰Y, ¹⁷⁷Lu, ²¹²Pb and ^{212/213}Bi for therapeutic applications. Of these, the positron-emitting ⁶⁴Cu radioisotope has garnered specific interest due to its favourable decay characteristics ($t_{1/2} = 12.7$ h; $\beta^+_{\max} = 0.655$ MeV; $\beta^-_{\max} = 0.573$ MeV) that allow simultaneous PET imaging and radiotherapy.^[55] Here, in addition to the emitted β^- particles,

Auger and conversion electrons can be exploited for enhancing the therapeutic efficacy.^[56] The β -emitting ^{67}Cu ($\beta_{\text{max}} = 0.577$ MeV, $t_{1/2} = 62$ h) is another highly attractive Cu radioisotope useful for therapeutic applications.

Metal-based radiopharmaceutical applications require chemically robust and radiolytically stable ligands, which can form radiometal complexes of high thermodynamic stability and kinetic inertness. For TACN derivatives, their radiocopper complexation ability is greatly influenced by the number and type of substituents on the macrocyclic ring. The formed metal complexes show a broad variability in their complexing properties, and present Cu(II) coordination chemistry similar to their non-radioactive counterpart (Table 1 and Figure 9). The pristine tridentate TACN ligand forms a highly stable Cu(II) complex ($\log K_{\text{Cu(II)-TACN}} = 15.52$), with a 1:1 Cu(II):TACN stoichiometry. When pyridylmethyl pendants are introduced onto the TACN backbone (e.g., **24–26** in Figure 8), the stability of Cu(II) complex is further increased due to the pendant arm coordination to the metal centre. For the complex of the trisubstituted TACN derivative, Cu(II)-**25**, formation constant ($\log K_{\text{Cu(II)-25}}$) is 27.4, which is similar to that for Cu(II)-cyclam and Cu(II)-cross-bridged cyclam complexes ($\log K \approx 27.1$).^[57–58] A pyridylmethyl side-arm when replaced with carboxylate functionality, as in **26**, provides site for further attachment of vector molecules for pharmaceutical targeting. Complex Cu(II)-**26** ($\log K_{\text{Cu(II)-26}} > 25$), in particular, exhibits very high in vivo stability after ^{64}Cu -radiolabelling.^[59] However, any further substitution of pyridylmethyl pendant leads to a decrease in stability of the complexes.^[60–61]

Of the picolinate-bearing TACN ligands, the Cu(II) complex of the monopicolinate derivative, Cu(II)-**34**, has the highest stability ($\log K_{\text{Cu(II)-34}} = 20.96$), also showing efficient ^{64}Cu -labelling.^[61] However, the stability of Cu(II) complexes decreases as additional picolinate arms are attached to the macrocycle. Similarly, the TACN-triphosphinate derivatives **28** and **29** (Figure 8) also yield $^{64}\text{Cu(II)}$ complexes with moderate stability⁶⁴ and sufficient kinetic inertness to allow PET imaging at early time points.^[62] NOTA derivatives are other well-studied TACN systems for radiolabelling. Their commercial availability, along with the ability to form very stable and kinetically inert ^{64}Cu -radiolabelled complexes under mild conditions, makes them almost ideal chelators for radiocopper. Quite recently, another promising class of TACN-based chelators featuring the imidazolyl (**30** and **31**) and the thiazolyl pendant (**32** and **33**) has been developed (Figure 8).^[63–64] These derivatives show fast and efficient radiolabelling (radiochemical yield > 95% within 30 min) with $^{64}\text{Cu(II)}$, even under mild conditions (pH 7.4, r.t). Interestingly, these complexes exhibit kinetic inertness comparable to the NOTA complex Cu(II)-**27**, which is more prone to demetalation/transchelation in the presence of an excess of the non-radioactive Cu(II), and under highly acidic conditions. In particular, Cu(II)-**33** shows an exceptionally long half-life of ~55 h. Notably, PET imaging studies in mice revealed a higher retention of $^{64}\text{Cu(II)-30–33}$ in the kidneys and liver compared with $^{64}\text{Cu(II)-NOTA/DOTA}$.

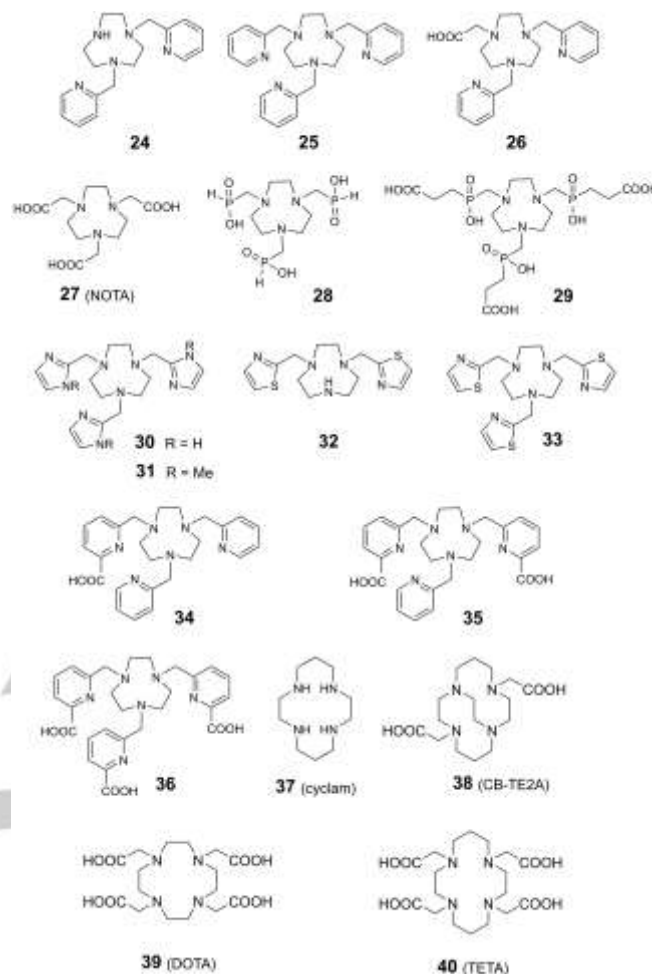


Figure 8. Structure of chelators for radiometals discussed in this work.

Bifunctional chelating agents (BFCAs)

TACN-based bifunctional chelating agents (BFCAs) have also been used for indirect radiolabelling of biomolecules, rendering them suitable for imaging and therapy. BFCAs serve the dual purpose of binding to the radionuclide efficiently and forming a highly stable complex, as well as of providing a functionality and/or site for attaching biological vectors. The linker connecting the biomolecule to the BFCa backbone helps to tune the lipophilicity, overall charge and aqueous solubility of the radiolabelled conjugate, and thus the overall biodistribution and pharmacokinetic properties. Figure 10 summarises the BFCAs used for copper radioisotopes. The Cu(II) complex of bromo-functionalised NOTA derivative, Cu(II)-**41**, has been used for antibody labelling.^[65] BFCAs possessing amino or carboxyl groups (e.g., **42**, **46–48**, **64** in Figure 10) have been developed for coupling to the biomolecules via peptide coupling protocols.^[66–70] One should note here that this strategy can only be applied provided that the stability of the radiometal complex is not harmed and steric restrictions do not occur. For example, maleimide-functionalisation in **44**, **49** and **63** enables attachment to biomolecules (e.g., peptide, antibodies, oligonucleotides) via a

stable thioether linkage with sulfhydryl groups.^[71-76] Similarly, isothiocyanate-functionalised TACN derivatives **45**, **50–54**, and **65** can be linked to amine-terminated biomolecules via very stable thiourea bonds.^[76-80] Over the last decade, clickable versions of BFCAs have also been used for tagging different biomolecules and nanoparticles to allow PET imaging using ⁶⁴Cu.^[81-84] Examples of these include ligands **55**,^[85] **56** and **60**^[86]

for rapid conjugation to specific peptides via Cu(I)-catalysed click reaction, and strained cyclooctyne featuring **57–59**^[82-84] for copper-free attachment to azide-functionalised peptides, proteins and nanoparticles. Also, tetrazine-bearing NOTA derivatives **61** and **62** have been employed for linking the *trans*-cyclooctene-functionalised antibodies using inverse-demand Diels-Alder reaction.^[87-88]

Table 1. Cu(II) complex formation constants (log $K_{Cu(II)-L}$) of TACN ligands.

Cu(II)-TACN	Cu(II)-25	Cu(II)-27	Cu(II)-28	Cu(II)-29	Cu(II)-32	Cu(II)-34	Cu(II)-35	Cu(II)-36
15.52 ^[89]	27.4 ^[60]	21.63 ^[90]	13.43 ^[91]	16.85 ^[92]	20.77 ^[64]	20.96 ^[60]	18.32 ^[60]	16.21 ^[60]

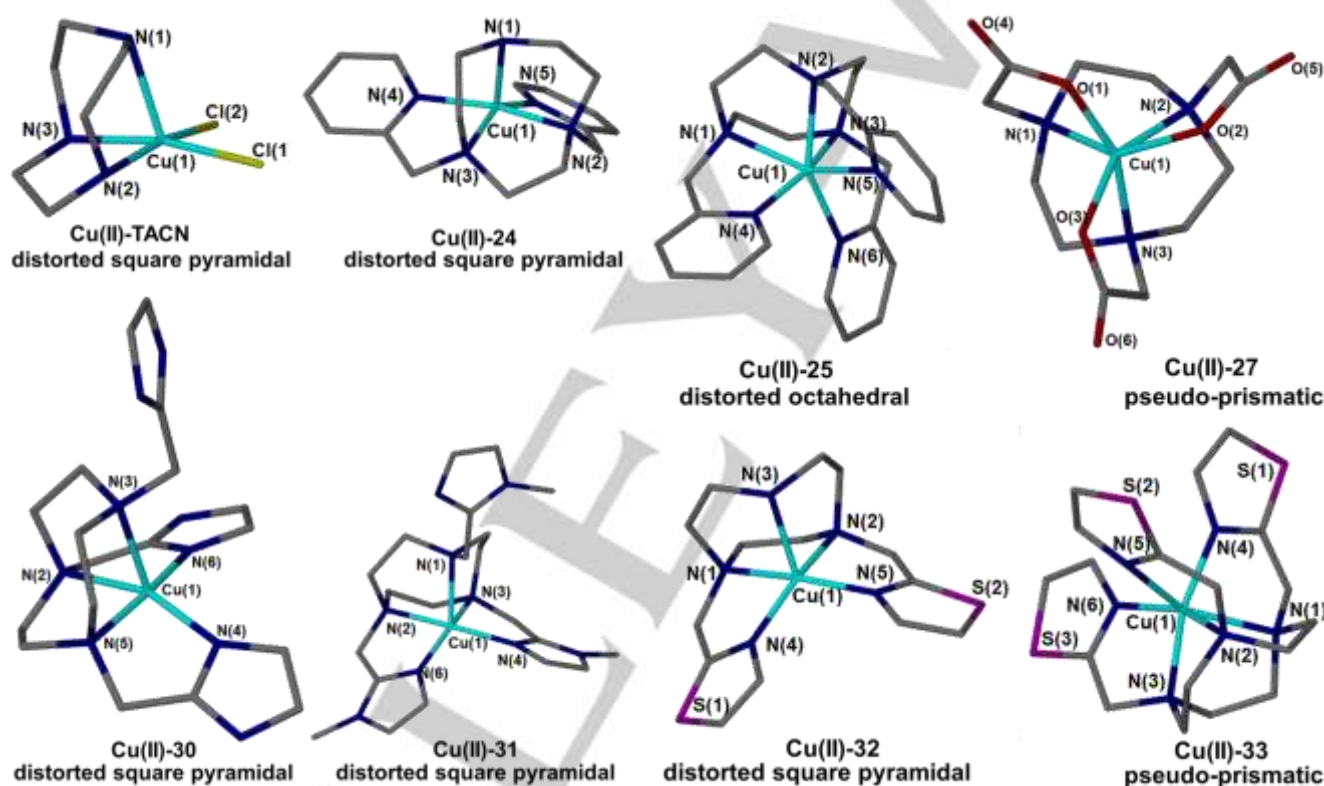


Figure 9. Cu(II) coordination geometry of TACN-based ligands.

The BFGA can be radiolabelled before or after its attachment to the biomolecule, using well-established protocols (Figure 11). However, the labelling should be rapid, efficient, and devoid of demanding purification steps. Moreover, to achieve exact quantitative biodistribution and pharmacokinetic data, it should be ensured that the radioisotope binds to the BFGA strongly as any radiometal leakage in living systems will lead to inaccurate determinations.^[63,93-94]

Owing to the favourable binding affinity of NOTA (**27**) for copper radioisotopes, *in vivo* studies have mostly been performed with ⁶⁴Cu(II) complexes of NOTA-attached

biomolecules and, derivatives thereof. For example, ⁶⁴Cu(II)-**27** was coupled to a bombesin (BBN) tetradecapeptide to target the gastrin-releasing peptide receptor (GRPR).^[95] Similarly, ⁶⁴Cu(II)-**27**-ML was developed for PACE4-targeted prostate cancer detection,^[96] ⁶⁴Cu(II)-**27**-KCCYSL for recognizing epidermal growth factor receptor (EGFR) rich breast carcinoma,^[97] ⁶⁴Cu(II)-**27**- α -MSH for melanoma imaging^[98] and ⁶⁴Cu(II)-**27**-HsTX1 for targeting the potassium channel.^[99] Moreover, seeking dual targeting, ⁶⁴Cu(II)-**47** derivatives equipped with peptides that target prostate-specific membrane antigen (PSMA) and GRPR-rich tumours have also been developed.^[100] Another NOTA

derivative, **61** (Figure 10), has been used for ^{64}Cu -radiolabeling of A33 antibody to evaluate a pre-targeting approach.

As Cu(II) complexes of 2-pyridylmethyl substituted TACN (**24**, Figure 9) show excellent in vivo stability, the ^{64}Cu (II)-**24**-BBN conjugate has been used to radioimage human prostate PC3 tumours, showing similar performance as the reported

analogues.^[101] Recently, TACN derivatives have also been grafted on different nanomaterials^[67,76,102-103] to develop nanoscale bioimaging platforms. For example, ligands **63–65** have been used to introduce Cu(II) binding motifs on dendritic polyglycerols (dPGs)-based bioactive and iron oxide nanoparticle-based imaging agents.^[67,76,102-103]

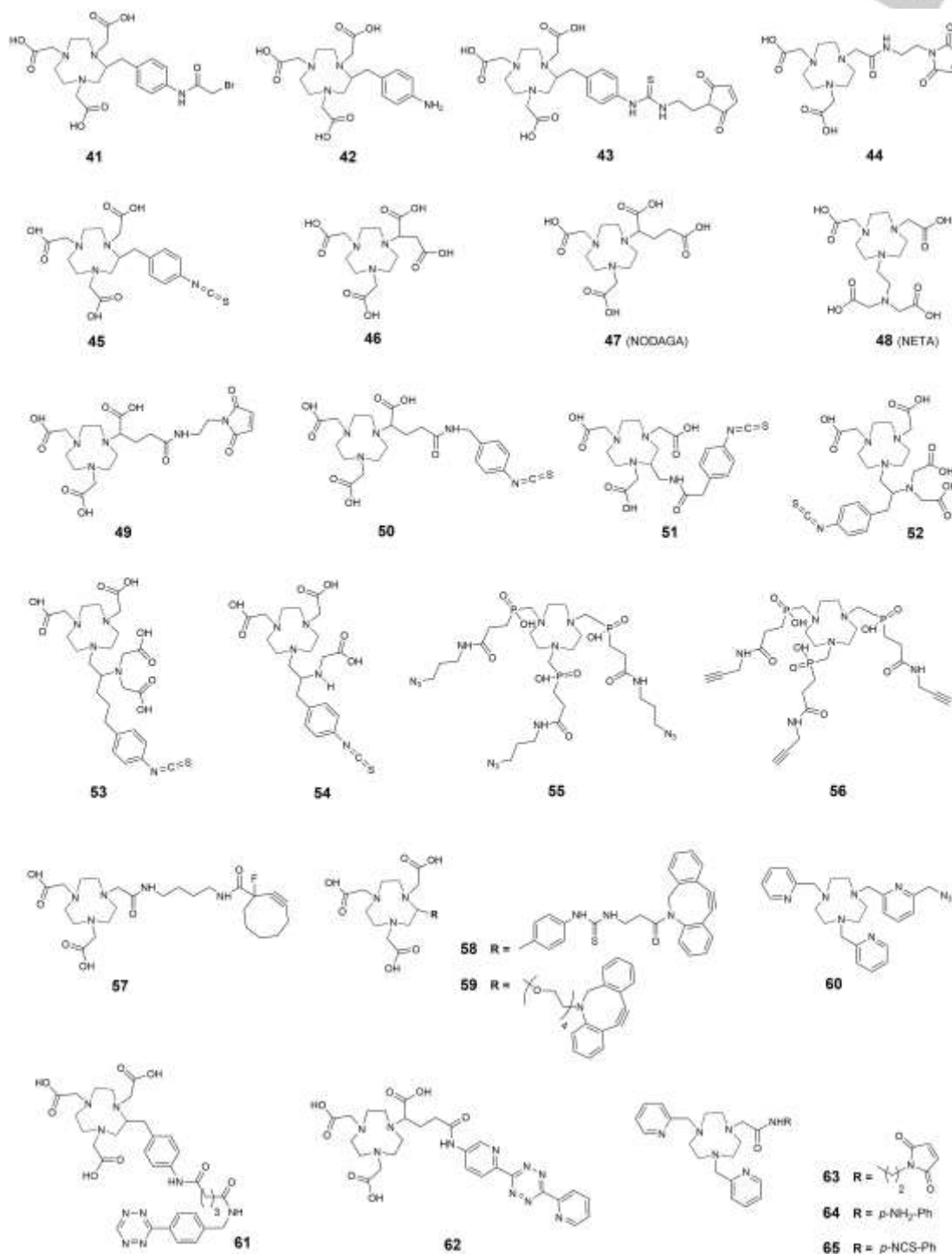


Figure 10. Examples of TACN-based bifunctional chelating agents (BFCAs) reported in the literature.

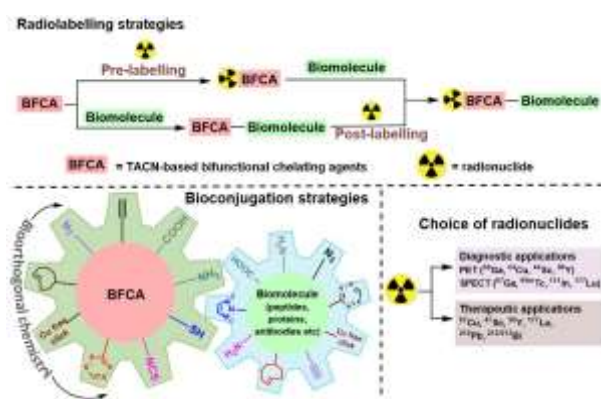


Figure 11. Strategies for the preparation of TACN-based radiolabelled BFCA-biomolecules.

Summary and Outlook

This minireview sheds light on the use of TACN-based molecular scaffolds for generating simplified mono- and polynuclear models for active sites of metalloenzymes, as well as chelators for metal-based radiopharmaceuticals. Tridentate coordination of TACN to metal ions leaves two or three vacant sites in the coordination sphere that can be exploited for mimicking the desired structural or functional aspects of the metal ion-binding biosite environment. Similarly, by applying principles of coordination chemistry, it is possible to tune the affinity of TACN-based ligands for radiometal ligation, as well as their availability for subsequent biomolecular functionalisation. Collectively, the examples presented herein provide a picture of how different substituents influence the coordination mode, functional properties, reactivity as well as in vivo stability of various TACN constructs and their transition metal complexes. With regards to the use of radiocopper labelled TACN derivatives for therapeutic applications, progress has been relatively slow due to the fact that there is currently a shortage of therapy-relevant ^{67}Cu radioisotope. However, with increasing availability of cyclotrons that can produce high-energy protons, and active engineering of new TACN motifs for ^{67}Cu binding, this situation is also most likely to change in the near future.

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MINIREVIEW

Coordination secured. Flexible coordination chemistry of TACN derivatives has been widely exploited for generating macrocyclic metal complexes as good mimics for metal-containing biosites and metal-based radiopharmaceuticals.



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Harnessing the Coordination Chemistry of 1,4,7-Triazacyclononane for Biomimicry and Radiopharmaceutical Applications