Poster

Solid and solution state structures of Cu(II) – macrochelates developed for theranostic purposes

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Radiometal-based radiopharmaceuticals offer a unique opportunity to diagnose, treat, and monitor many diseases, including cancer. While only a few radioactive metals have been used in recent decades due to difficulties in their production and purification, a wide variety of non-standard radionuclides are available today, offering a great choice in terms of decay energy and properties, and thus having the potential to improve theranostic (therapeutic and diagnostic) options. Radioactive metal ions must be securely bound to a chelating agent attached to a biologically active molecule to successfully deploy the radiation to a desirable molecular target. ^{64}Cu ($t_{1/2}$ = 12.7 hours) is suitable for both Positron Emission Tomography (PET) imaging and cancer therapy due to its unique decay profile, which combines β^+, β^- and electron capture emission. In addition, the ^{64}Cu isotope can be used together with the pure β^- emitter ^{67}Cu isotope (^{67}Cu, $t_{1/2}$ = 61.9 hours) providing a PET imaging pair. However, the in vivo stability of $^{64/67}$Cu(II) complexes can be thwarted by the presence of reducing agents in the biological medium, which may cause the reduction of Cu(II) to Cu(I). Since Cu(I) has a significantly different coordination preference than Cu(II) and is much more labile to ligand exchange, premature dissociation of the complex and release of the radionuclide may occur in a biological environment, posing a radiation hazard to healthy organs. So far, only a few attempts have been made to develop chelators that can safely bind both Cu(II) and Cu(I) forms with high stability and thus prevent this demetallation process. Our goal is to develop ligands that meet all the above criteria and can make the $^{64/67}$Cu radionuclide pair suitable for clinical use. We present here the structural results of a new family of polyazamacrocyclic chelators: DO4S [1], DO4NH$_2$, DO2A2S [1], CB-TE2S, PyDO2S, TE4S [2] (Figure 1a). The structures of Cu(II) complexes were studied in solid state by single crystal X-ray diffraction (SC-XRD). In the case of substances with biological uses, it is also important to know the structures formed in solution. The room temperature and frozen solution-state structures were investigated by electron spin resonance (ESR) spectroscopic methods. We have found that the coordination number and the formed geometry can vary greatly depending on the position of the ligand donor atoms (Figure 1b,c). In many cases, coordination isomers can also appear in solution, the distinction of which is a great challenge even with modern large-scale structural analysis methods due to small spectroscopic differences.

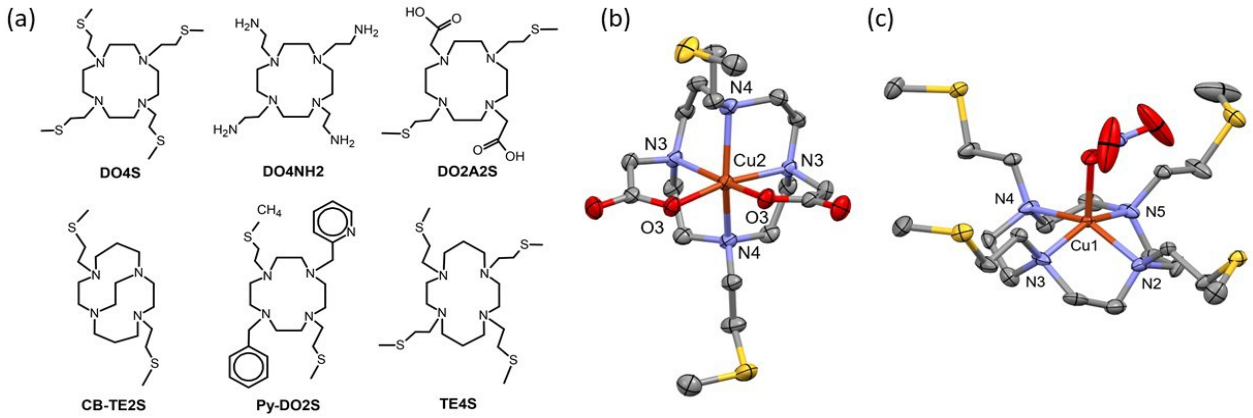

Figure 1. (a) Structure of the investigated macrochelate ligands and structure of the Cu(II)-complexes in single crystals of (b) [Cu(DO2A2S)] and (c) [Cu(DO4S)(NO_3)]•NO_3 with octahedral and pentahedral coordination, respectively.

[1] Tosato, M., Dalla Tiezza, M., May, N. V., Isse, A. A., Nardella, S., Orian, L., Verona, M., Vaccarin, C., Alker, A., Mäcke, H., Pastore, P., Di Marco, V. (2021) *Inorg. Chem*., **60**, 11530.

[2] Tosato, M., Pelosato, M., Franchi, S., Isse, A. A., May, N. V., Zanoni, G., Mancin, F., Pastore, P., Badocco, D., Asti, M., Di Marco, V. (2022) *New. J. Chem*., **46**, 10012.

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