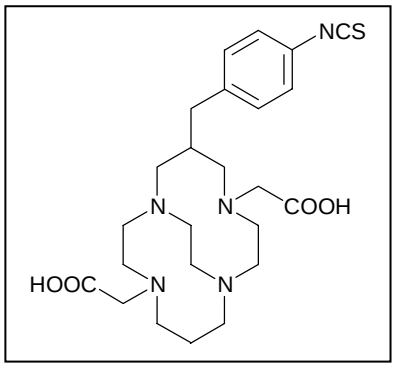
Ultrastable Complexes for *In Vivo* Use: A Bifunctional Chelator Incorporating a Cross-Bridged Macrocycle

Elizabeth A. Lewis,[1] Cheryll C. Allan,[1] Jon D. Silversides,[1] Karen A. Smith,[2] Ross W. Boyle,[1] John Greenman[2] and Stephen J. Archibald[1,*]

[1]*Chemistry Department and* [2]*Medical Research Laboratory, University of Hull, Hull, HU6 7RX, (UK)*

There is much current interest in the development of bifunctional chelators (BFCs) for the labeling of biomolecules with copper(II) radionuclides for diagnostic imaging and targeted radiotherapy.[1] The ability of the BFC to bind and retain the copper(II) ion allowing its localization at the target site and limiting its potentially harmful release elsewhere in the body is crucial. Consequently, there is an ongoing requirement for the development of novel, high stability copper(II) chelators for bioconjugation.

Recent research efforts have focused on the use of systems based on 1,4,8,11-tetraazacyclotetradecane tetraacetic acid (TETA) with clinical trials in progress. However, there is evidence of transchelation from radiometal labeled TETA-bioconjugates *in vivo*.[2] An analogue of TETA, in which two non-adjacent nitrogen atoms are linked by an ethylene bridge (so-called 'cross-bridged' macrocycle) exhibits far greater complex stability and overcomes these problems.[3] Herein we present the synthesis of a novel BFC incorporating a cross-bridged macrocycle and its reactivity towards copper(II). An isothiocyanate derivative has been prepared that forms a thiourea linkage with the primary amine groups of biologically relevant molecules. Current progress of conjugation studies with biotin, BSA and antibody fragments in order to evaluate the compounds *in vitro* serum stability and cell targeting ability is also reported.



1. C. J. Anderson, M. A. Green and Y. Fujibayashi in *Handbook of Radiopharmaceuticals*, M. J. Welch and C. S. Redvanly Eds., John Wiley & Sons Ltd., New York 2003, pp.401-422
2. L. A. Bass, M. Wang, M. J. Welch and C. J. Anderson, *Bioconjugate Chem.*, 2000, **11**, 527
3. C. A. Boswell, X. Sun, W. Nui, G. R. Weisman, E. H. Wong, A. L. Rheingold and C. J. Anderson, *J. Med. Chem.*, 2004, **47**, 1465; E. A. Lewis, R. W. Boyle and S. J. Archibald, *Chem Commun*., 2004, 2212