Novel use of rigidified tetraazamacrocycles as tumour targeted prochelators

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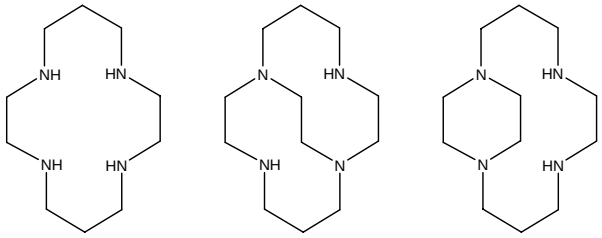
Chelators of radioisotopes have been routinely incorporated into tumour specific targeting strategies in order to deliver suitable radioactivity into malignant tissues. It is known that macrocylic chelators have enhanced *in vivo* stability over acyclic chelators such as DTPA.

Copper is a suitable radiometal for diagnostic imaging and therapeutic applications. ^{64}Cu (β^+ (19%), β^- (40%), $t_{½}$ = 12.7 hr) has appropriate decay characteristics to utilize positron emission tomography for diagnostic imaging, while ^{67}Cu (β^- (100%), $t_{½}$ = 63 hr) can be used to destroy tumour cells for therapeutic purposes.

Cyclam (1,4,8,11-tetraazacyclotetradecane) (**1**) is a suitable macrocyclic chelator as its cavity size is appropriate for accommodation of copper(II) ions. Rigidification of the macrocycle by addition of an ethylene 'bridge' leads to complexes with higher kinetic stability. This ethylene bridge can be inserted between adjacent or non-adjacent nitrogen atoms, leading to the 'cross-bridged' (**2**) and 'side-bridged' (**3**) analogues of cyclam.



A novel use of these structurally rigidified macrocycles would lie in the strategy of selective tumour targeting. Conjugation of these bridged macrocycles to a tumour targeting moiety would produce a prochelator for delivery of metal ions into tumours.

Folate receptors are overexpressed on several malignancies, greatly increasing the amount of folates internalized into the tumour cells by receptor mediated endocytosis. By conjugating a rigidified cyclam to a folate derivative, it is highly likely that the entire macrocyclic copper complex would be internalized into neoplastic tissues with a high target to non-target ratio. By utilizing copper radionuclide, the combination of targeting and chelating moieties leads to a potential family of radiopharmaceuticals for use against cancers.

1. Boswell CA, Sun XK, Niu WJ, Weisman GR, Wong EH, Rheingold AL, Anderson CJ, J. Med. Chem. 47 (2004) 1467-1474
2. Lewis EA, Boyle RW, Archibald SJ, Chem. Comm. (2004) 2212-2213