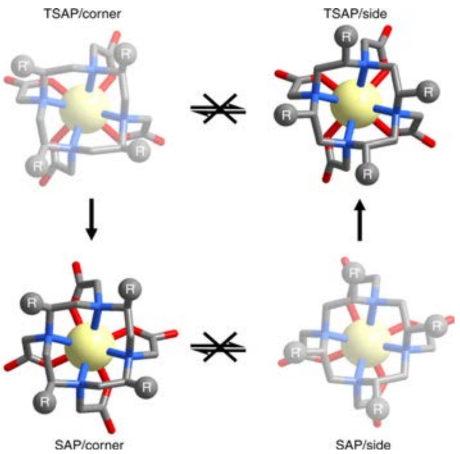
Chiral Cyclen Compounds and Their Uses

Dr. Ga-lai LAW
Department of Applied Biology and Chemical Technology

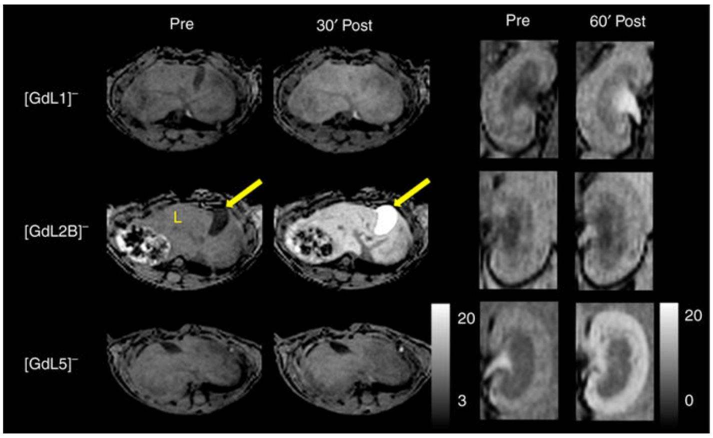
Biological Imaging

. Chiral DOTA . MRI Contrast Agent . PET Contrast Agent . Radiometal Chelators .

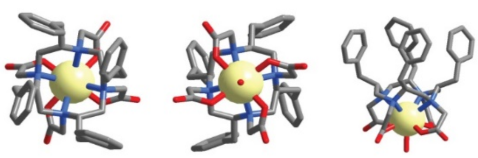
Despite established clinical utilization, there is an increasing need for safer, more inert gadolinium-based contrast agents, and for chelators that react rapidly with radiometals. Here we report the syntheses of a series of chiral DOTA chelators and their corresponding metal complexes, and reveal properties that transcend the parent DOTA compound. We incorporated symmetrical chiral substituents around the tetraaza ring, imparting enhanced rigidity to the DOTA cavity, enabling control over the range of stereoisomers of the lanthanide complexes. The Gd chiral DOTA complexes are shown to be orders of magnitude more inert to Gd release than [GdDOTA]-. These compounds also exhibit very fast water exchange rates in an optimal range for high field imaging. Radiolabeling studies with (Cu-64/ Lu-177) also demonstrate faster labelling properties. These chiral DOTA chelators are alternative general platforms for the development of stable, high relaxivity contrast agents, and for radiometal complexes used for imaging and/or therapy.



Restricted isomerism of $[GdL3]^-$. Four stereoisomers are possible for $[LnDOTA]^-$, but two of these structures are inaccessible with our system, they are represented by the washed out structures. SAP/corner and TSAP/side structures derived from the partial solved crystallographic data of **$[GdL3]^-$**; R represents the chiral substituent. Atom labels: C (grey), N (blue) and O (red)



MR imaging in mice. Dynamic T_1-weighted MR images at 4.7 tesla in C57/Bl6 mice before, after 0.1 mmol per kg injection of **$[GdL1]^-$**, **$[GdL2B]^-$** and **$[GdL5]^-$**. Axial images of the liver (L) and gall bladder (arrow) coronal images of the kidneys highlighting the differences in elimination route and organ enhancement among the complexes



Crystal structure of **$[GdL4]^-$** from top view, bottom view and side view. Atom labels: C (grey), N (blue), and O (red)

Representative Publication:

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Contact Us
Ms. Nelly Lam . Manager
T // (852) 3400 2819
E // nelly.lam@polyu.edu.hk