

Supporting Information

Synthesis, ^{64}Cu -labeling and PET imaging of 1,4,7-triazacyclononane derived chelators with pendant azaheterocyclic arms

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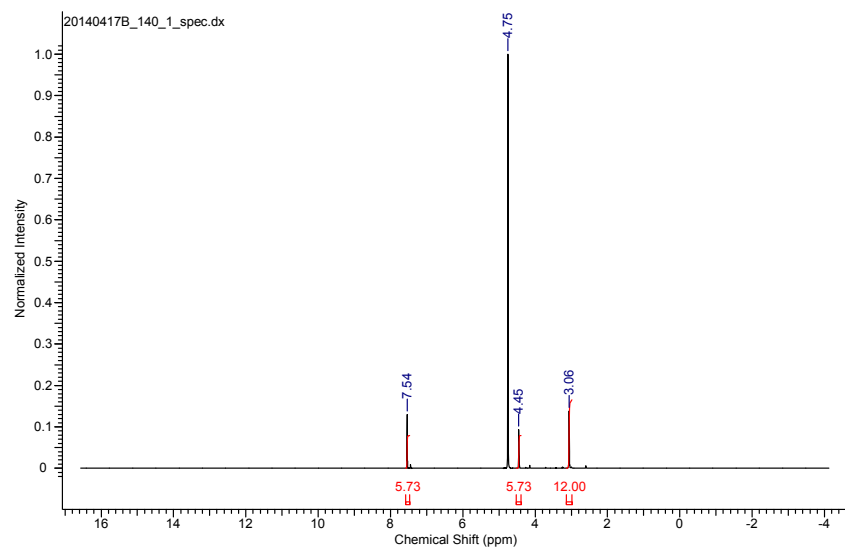
* Corresponding author: MDB, Hugstetterstr. 55, 79106 Freiburg, Germany. E-mail: mark.bartholomae@uniklinik-freiburg.de.

Content

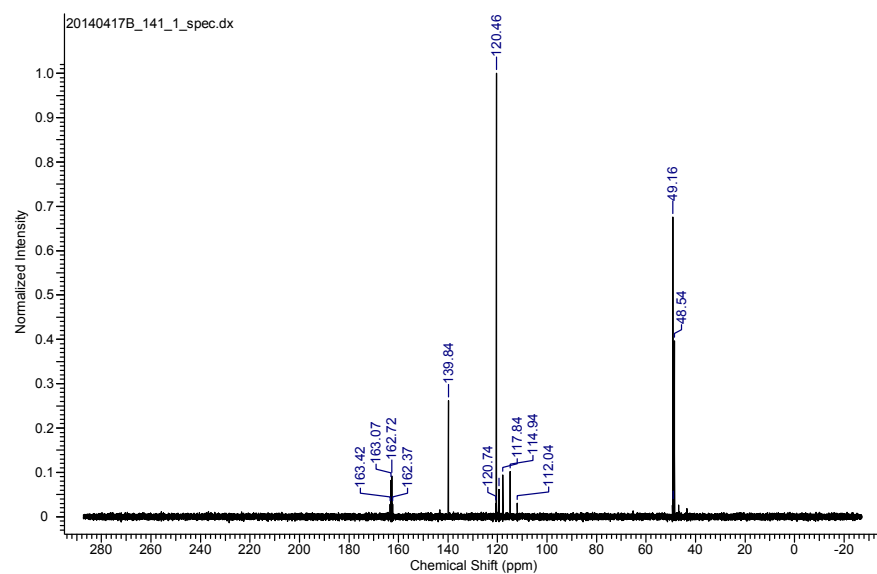
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NMR Measurements

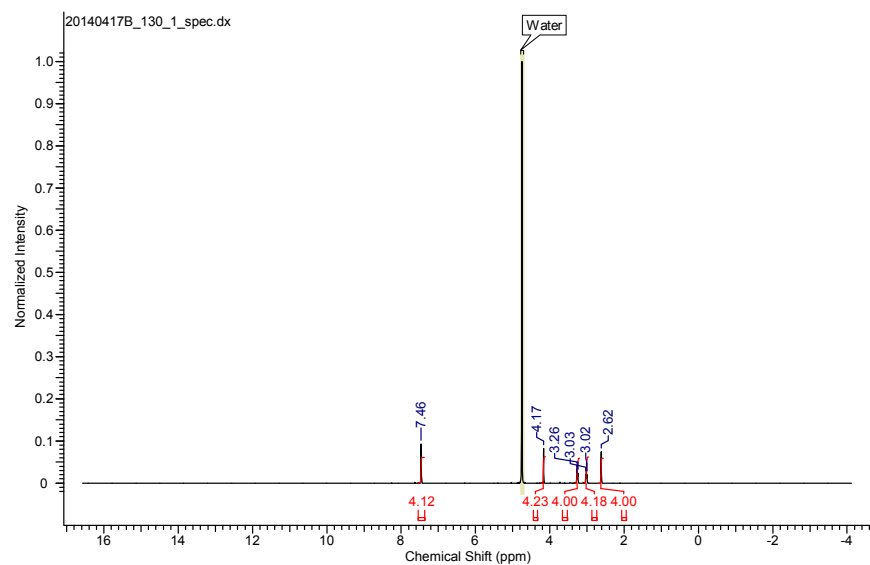
^1H NMR NOTI



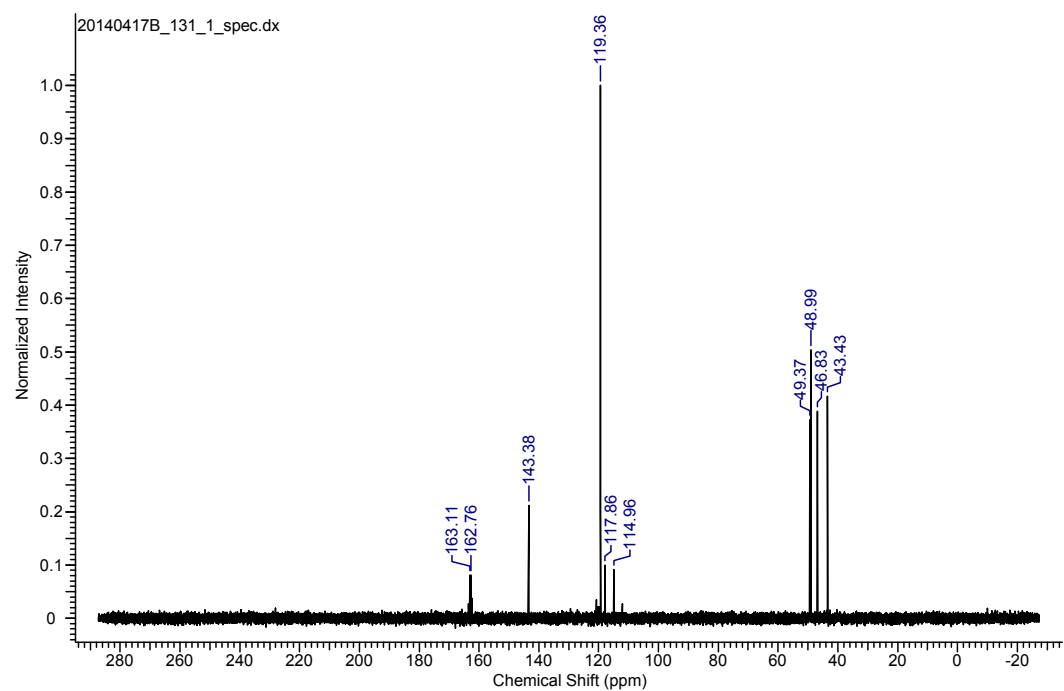
^{13}C NMR NOTI



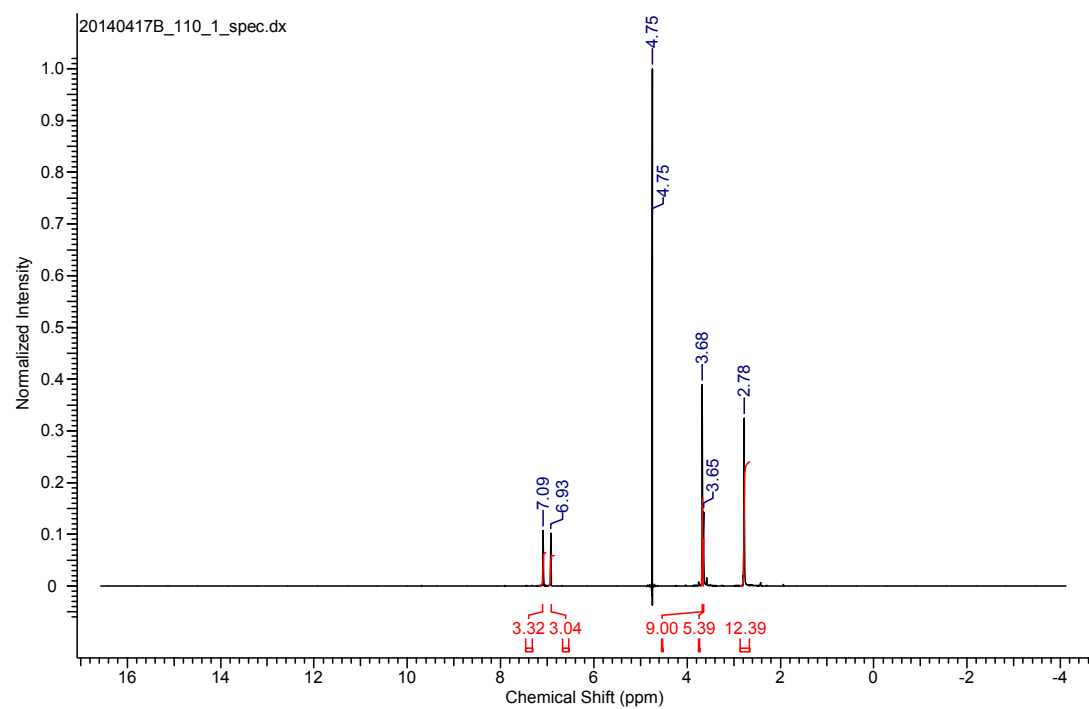
¹H NMR NODI



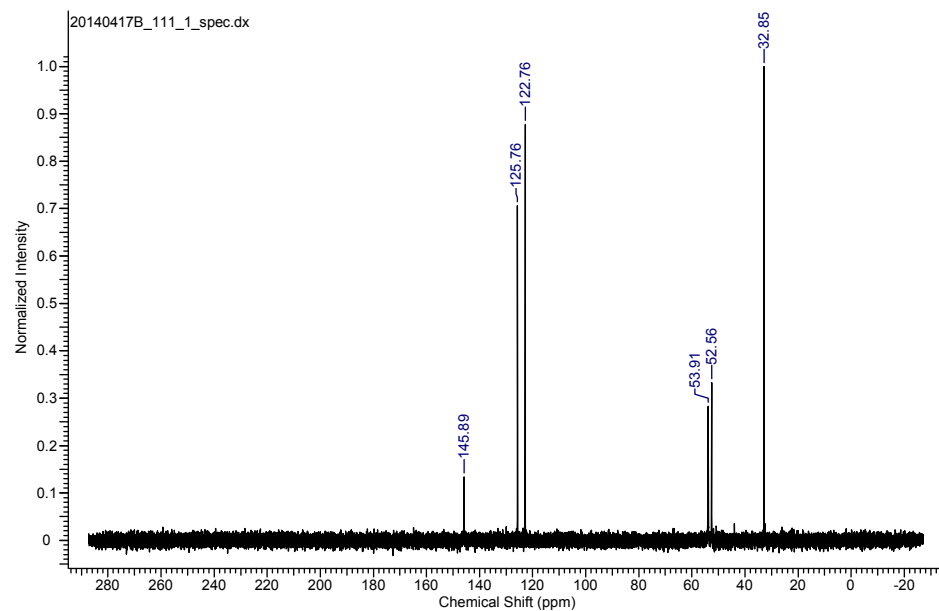
¹³C NMR NODI



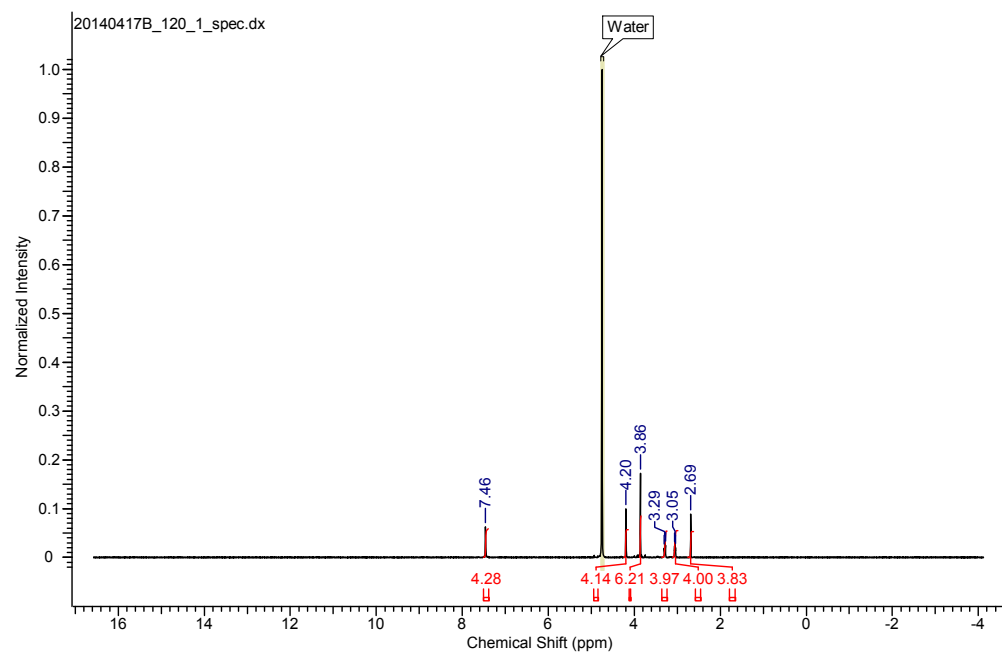
¹H NMR NOTI-Me



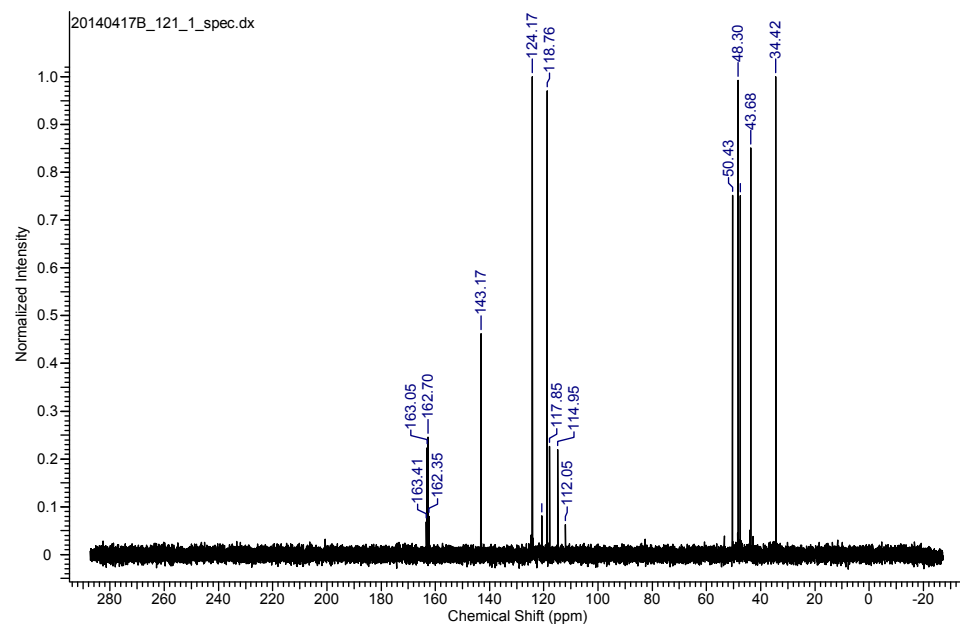
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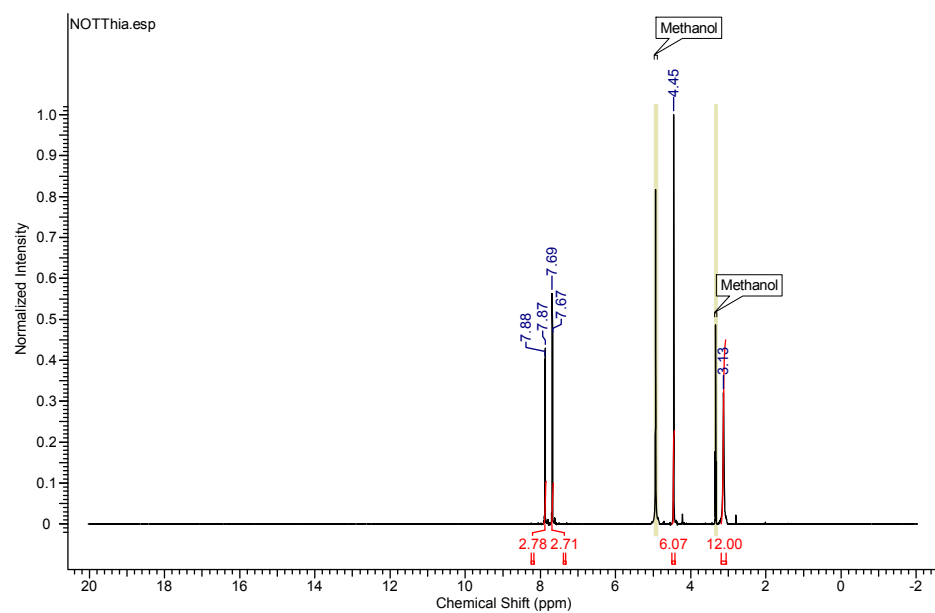
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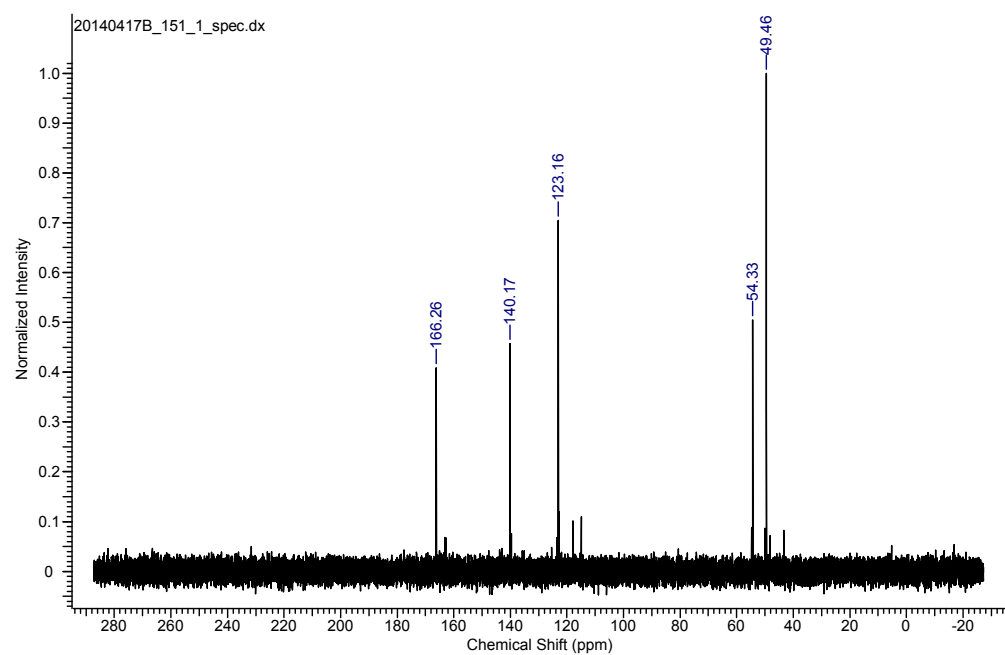
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¹H NMR NOTThia

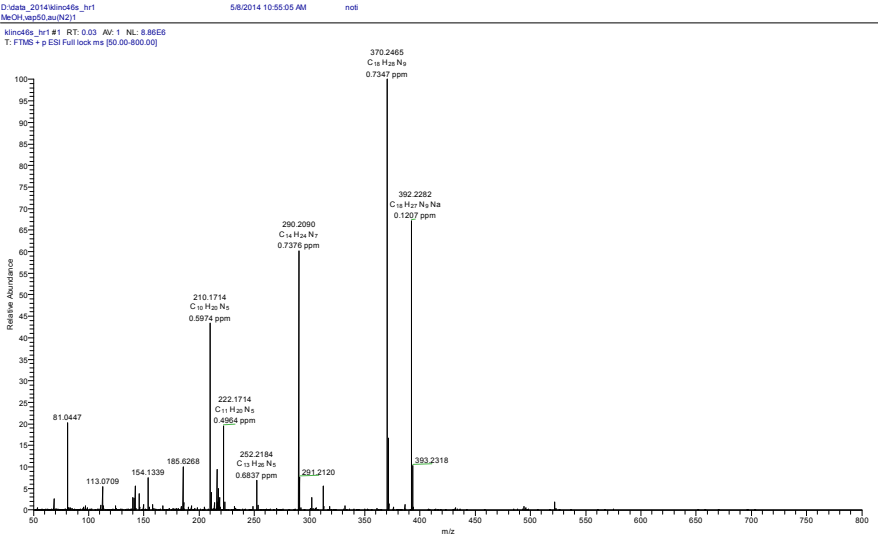


¹³C NMR NOTThia

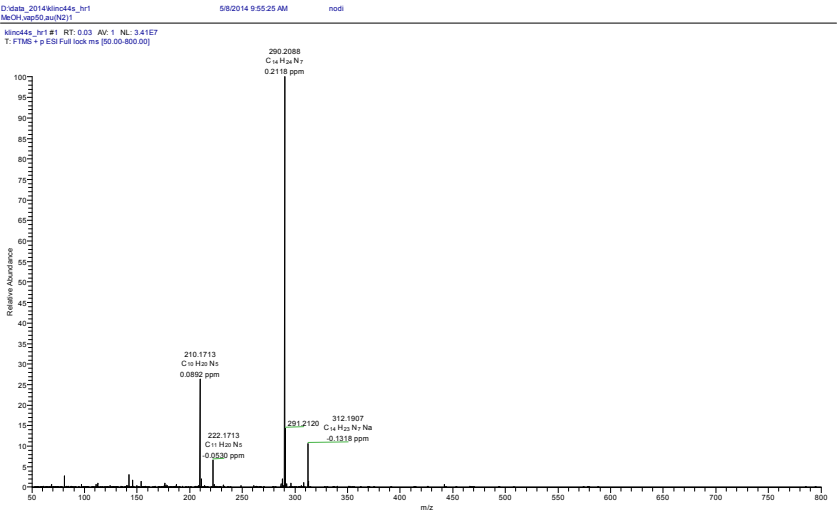


MS Data Chelators

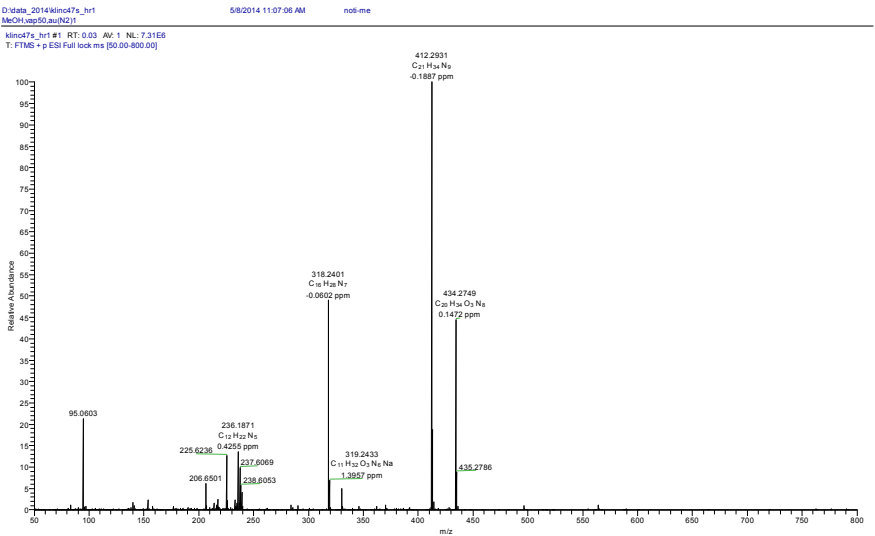
NOTI



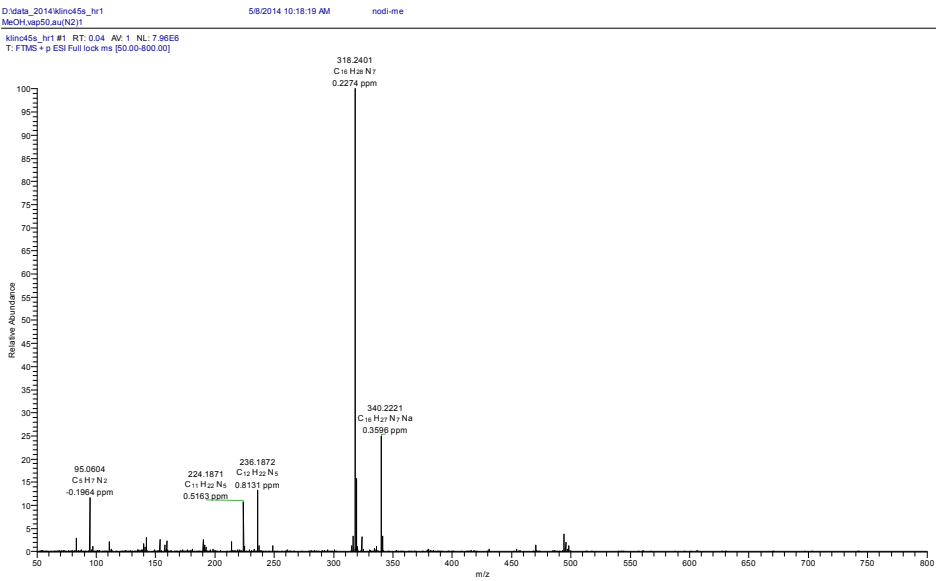
NODI



NOTI-Me



NODI-Me



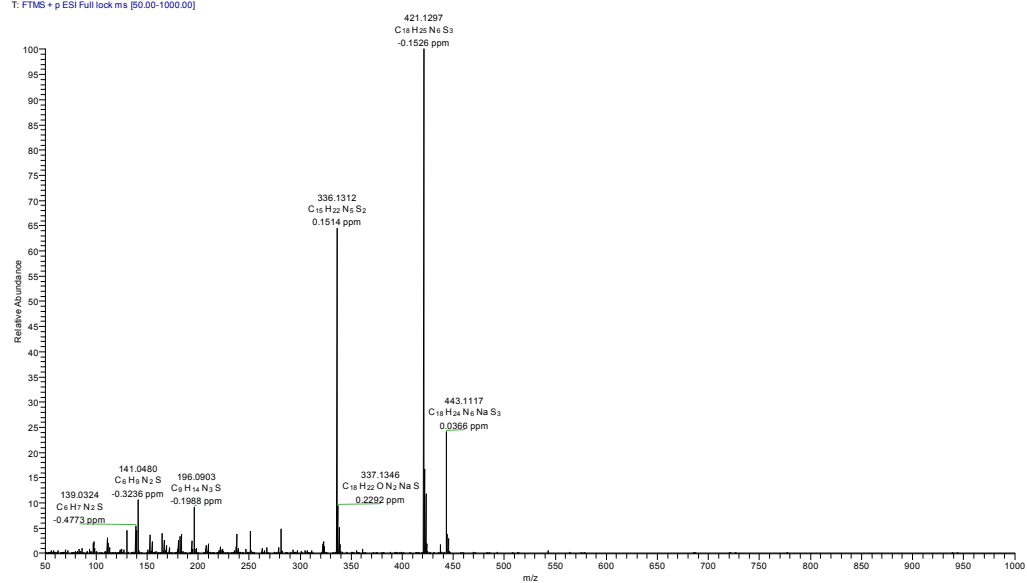
NOTThia

D:\data_2014\kinc50s_hr2

5/20/2014 12:13:26 PM

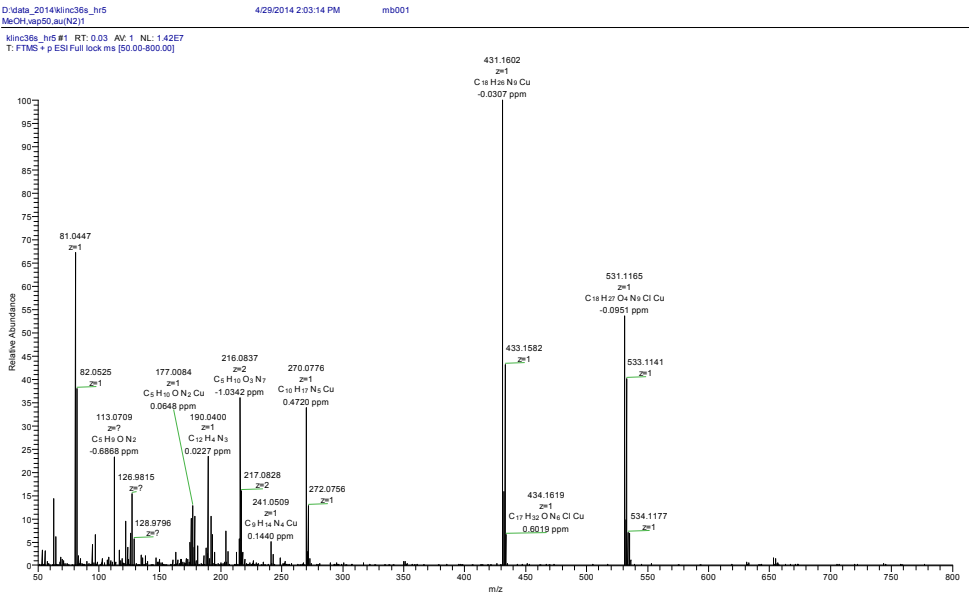
notthia

kinc50s_hr2 #1 RT: 0.03 AL: 7.39E6
T: FTMS - p ESI Full lock.ms [50.00-1000.00]

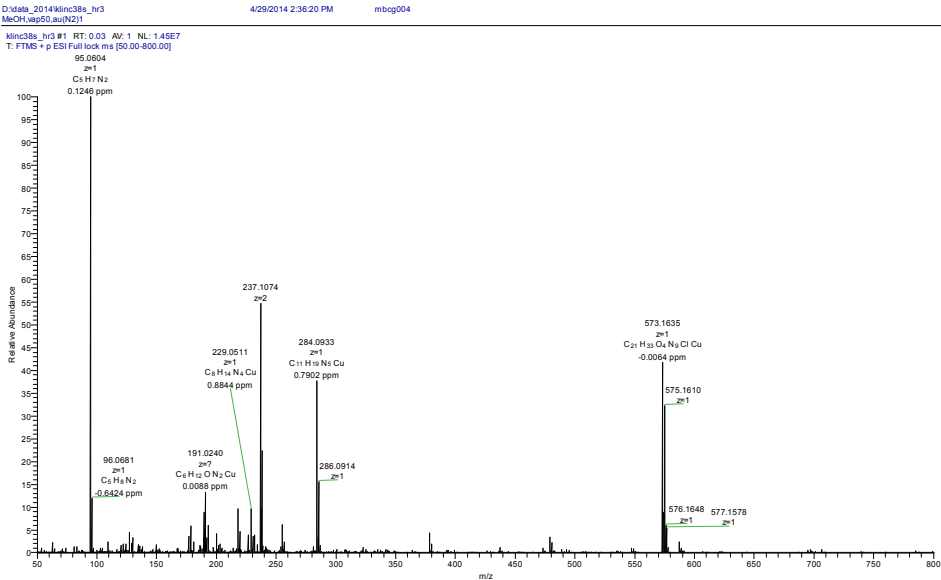


MS Data Complexes

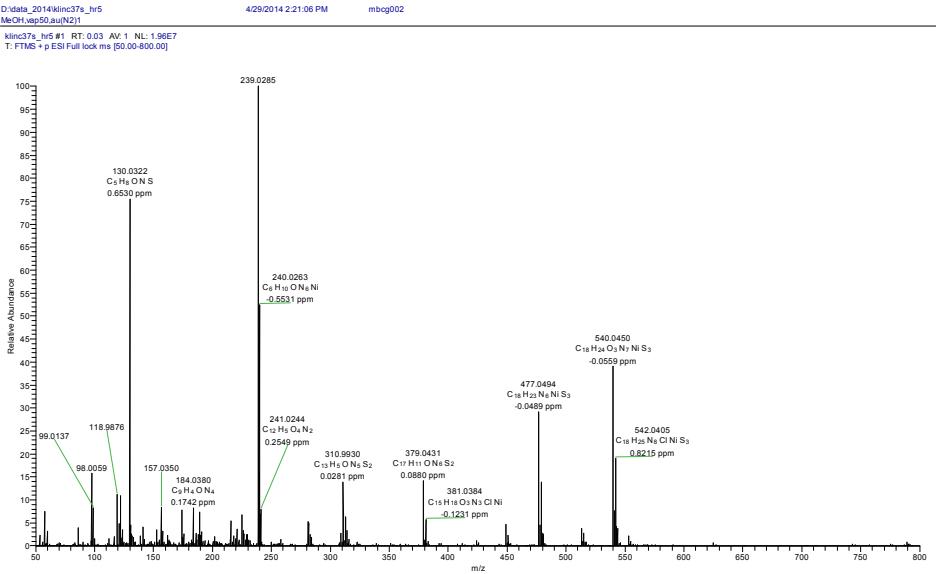
[Cu(NOTI)H](ClO₄)₃· 1.3 H₂O (Cu-1)



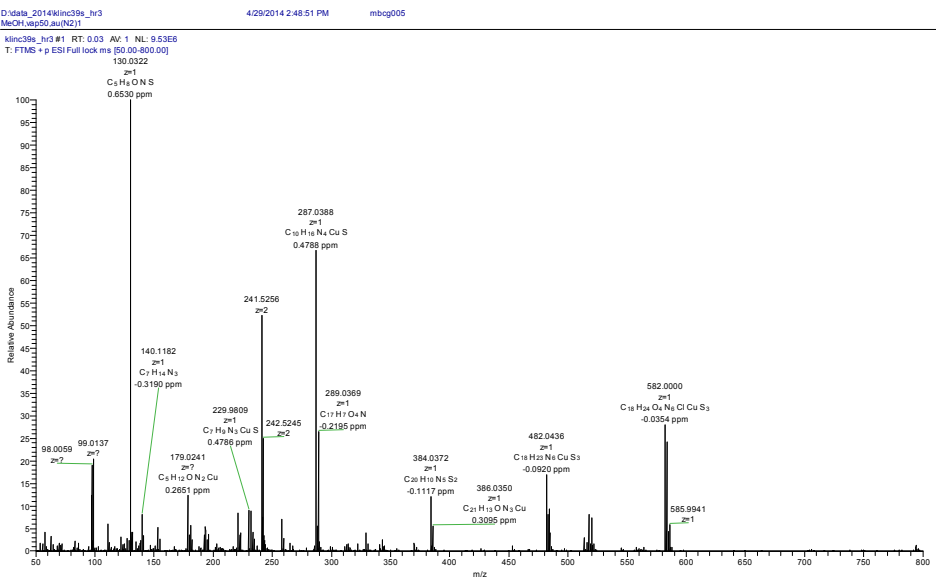
[Cu(NOTI-Me)H]₂(ClO₄)₅· 2TFA · 4H₂O (Cu-2)



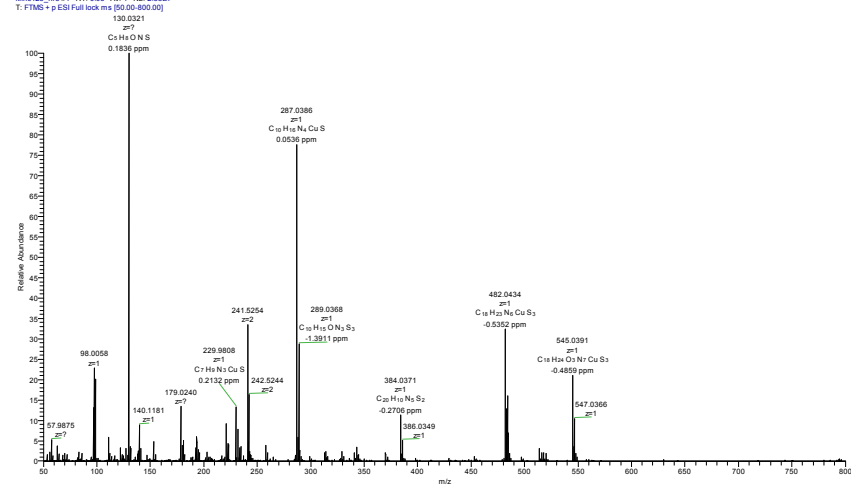
[Cu(NOTI-Me)](BF₄)₂ (Cu-3)



[Cu(NOTThia)](ClO₄)₂ (Cu-4)

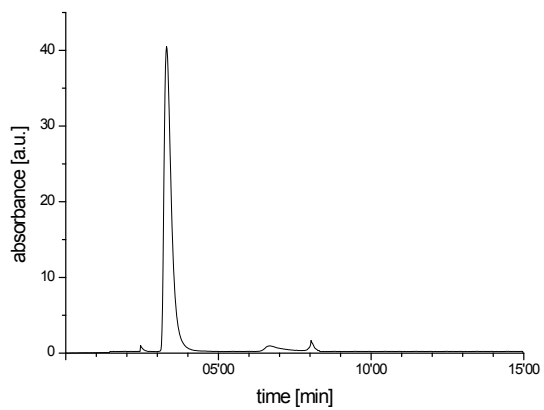


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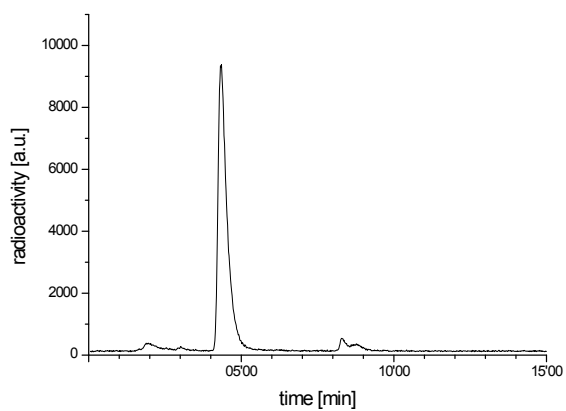
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HPLC Data Complexes

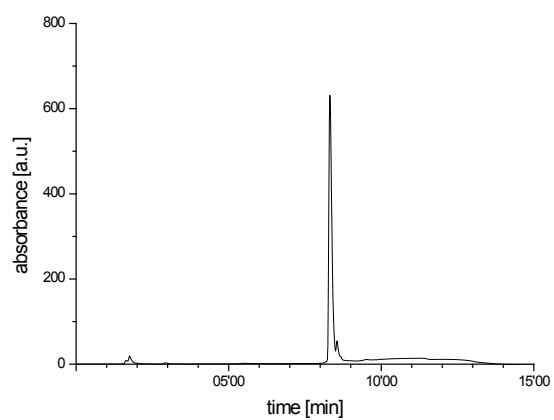
Cu nat. NOTI



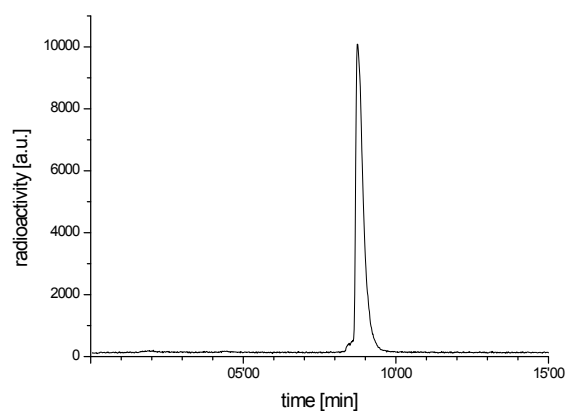
^{64}Cu NOTI



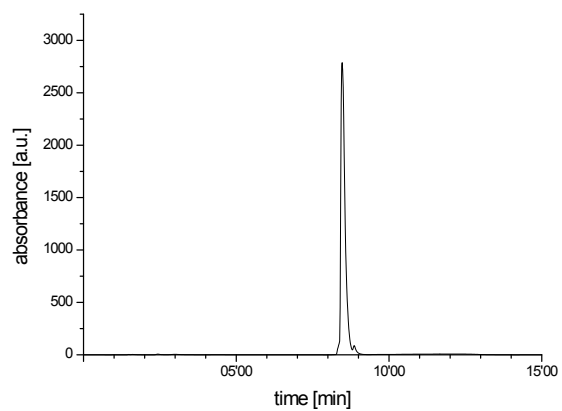
Cu nat. NOTI-Me



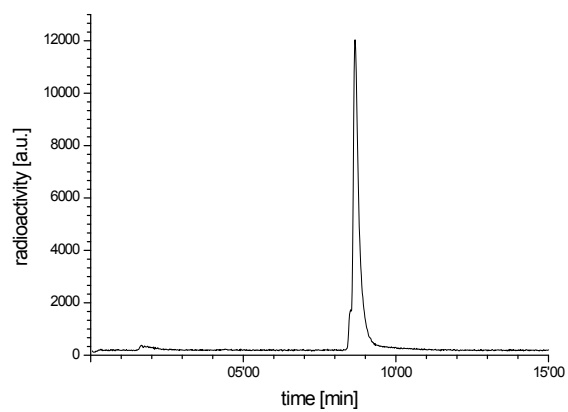
⁶⁴Cu NOTI-Me



Cu nat. NOTThia

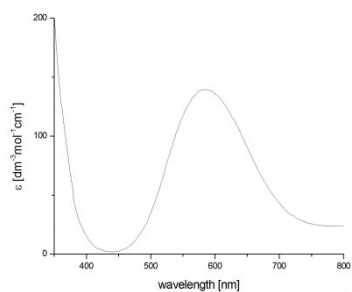


⁶⁴Cu NOTThia

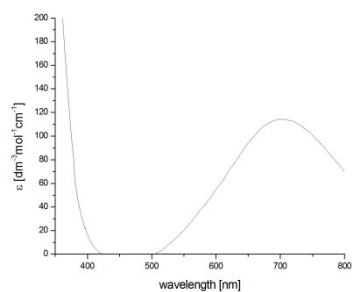


Electronic spectra Cu nat. complexes

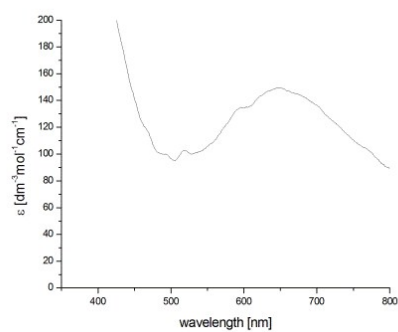
Cu nat. NOTI



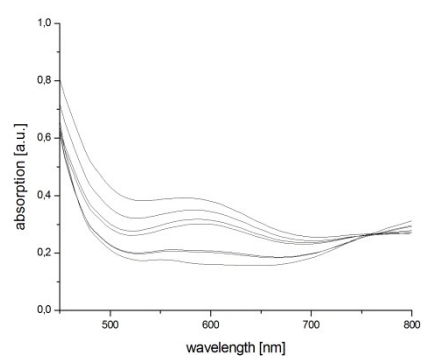
Cu nat. NOTI-Me



Cu nat. NOTThia

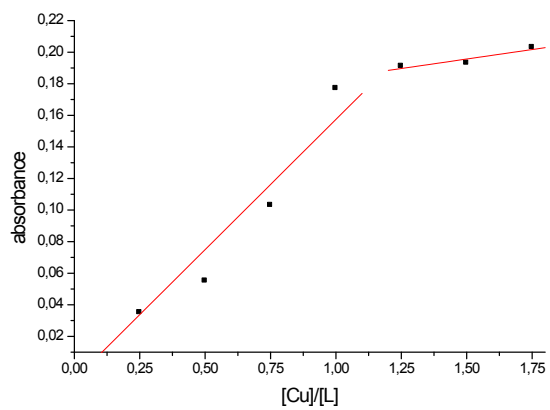


Cu NOTThia 5M HCl challenge

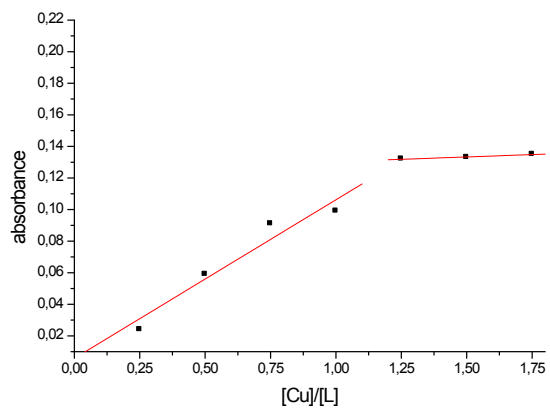


UV/vis titration experiments

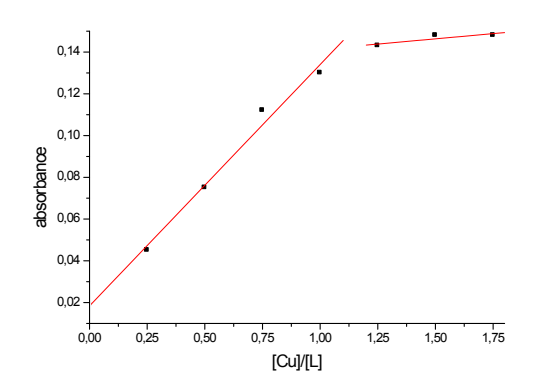
NOTI



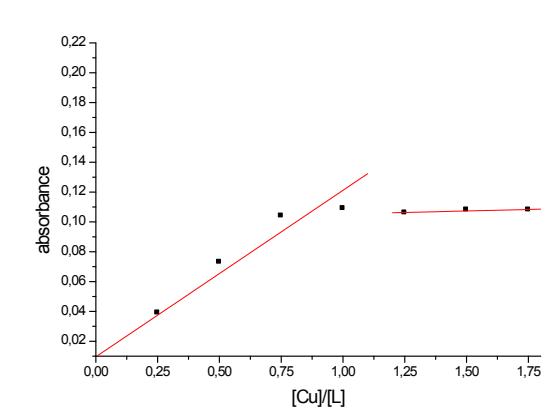
NOTI-Me



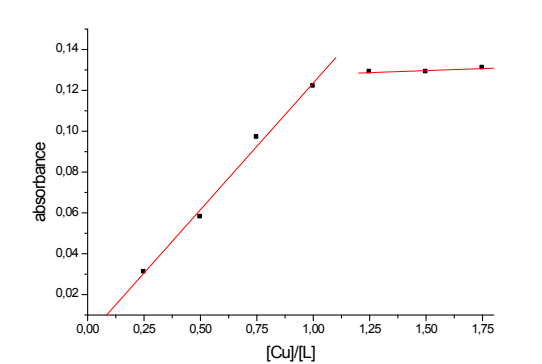
NOTThia



DOTA



NOTA

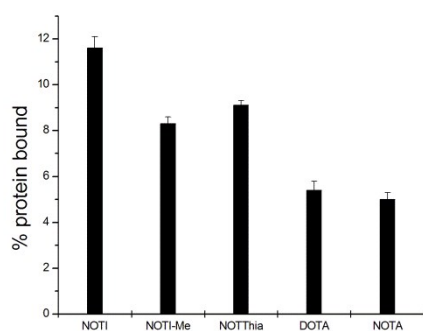


Radiochemical yield

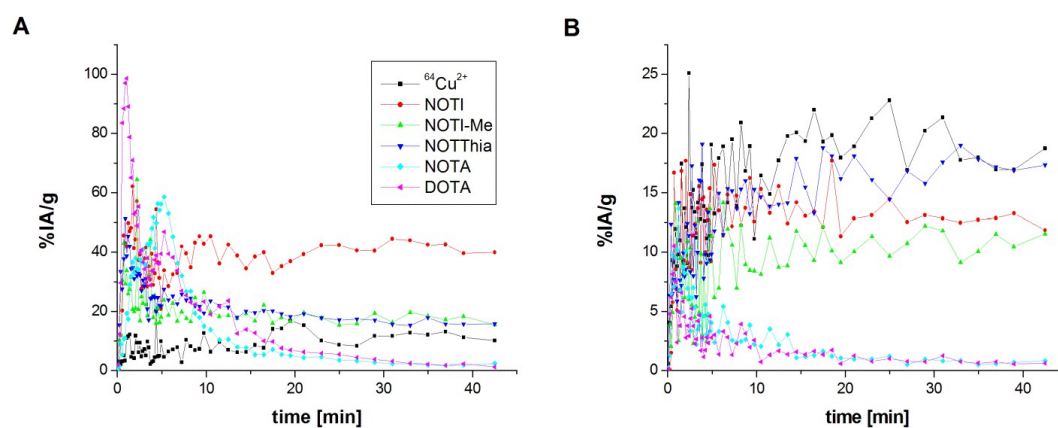
⁶⁴ Cu labeling experiments of NOTI, NOTI-Me, NOTThia, NOTA and DOTA. ^[a]				
Ligand	pH 4 ^[b]	pH 5.5 ^[c]	pH 7.4 ^[d]	pH 8.0 ^[e]
NOTI	96.0 ± 0.4%	92.9 ± 0.2%	95.4 ± 1.1%	99.9 ± 0.6%
NOTI-Me	98.2 ± 0.7%	93.4 ± 4.4%	96.3 ± 0.7%	98.6 ± 0.3%
NOTThia	95.8 ± 1.2%	87.4 ± 0.1%	98.0 ± 0.7%	97.0 ± 0.5%
NOTA	97.2 ± 1.0%	12.0 ± 0.2%	54.4 ± 3.6% ^[f]	-
DOTA	45.8 ± 2.8%	5.9 ± 0.1%	81.5 ± 6.1% ^[f]	93.7 ± 1.6% ^[f]

[a] Unless otherwise stated c(L) = 1 μM, r.t., 1 min; all buffers c = 0.1M. [b] Na-acetate. [c] MES. [d] HEPES. [e] NH₄OAc. [f] c(L) = 5 μM, 95°C, 30 min.

Percentage ⁶⁴Cu complex activity associated with serum proteins



Time-activity curves of PET scans in nude mice



A = kidneys, B = liver

Auxiliary information on X-ray structures

CCDC 1043399 (Cu-1), CCDC 1043400 (Cu-22), CCDC 1043398 (Cu-3), CCDC 1043401 (Cu-4) and CCDC 1043403 (Cu-5) contain the supplementary crystallographic data for this paper, including coordinates, experimental details, refinement instructions and structure factors. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)-336-033; e-mail: deposit@ccdc.cam.ac.uk), or online *via* www.ccdc.cam.ac.uk/data_request/cif

Refinement of [Cu(NOTI)H](ClO₄)₃·1.3 H₂O (Cu-1)

The structure exhibits isolated hydrogen-bond networks running through a perchlorate anion, the protonated imidazole group, a water molecule and a second anion. 70:30 disorder in the imidazolium group consequently also affects the hydrogen-bonded moieties (Fig. S 1). Only the minor domain provides enough space for a second water molecule, hence the stoichiometry of 1.3. Accordingly, the calculated solvent accessible void vanished after assigning the highest remaining residual peak to oxygen, with a site occupation factor tied to the minor part of the disorder. Hydrogen atom of the 30% occupied water site were not found on the difference Fourier map and have not been assigned in the model.

The remaining two imidazole groups bound to copper both participate in additional hydrogen bonds with a ClO₄⁻ on each side (N...O distances: 2.955(4) and 2.897(4) Å), forming infinite zig-zag chains alternating between perchlorate anion and complex cations (not shown). At the unoccupied coordination site of the Cu center, only a van-der-Waals contact with a ClO₄⁻ is found (2.924(2) Å).

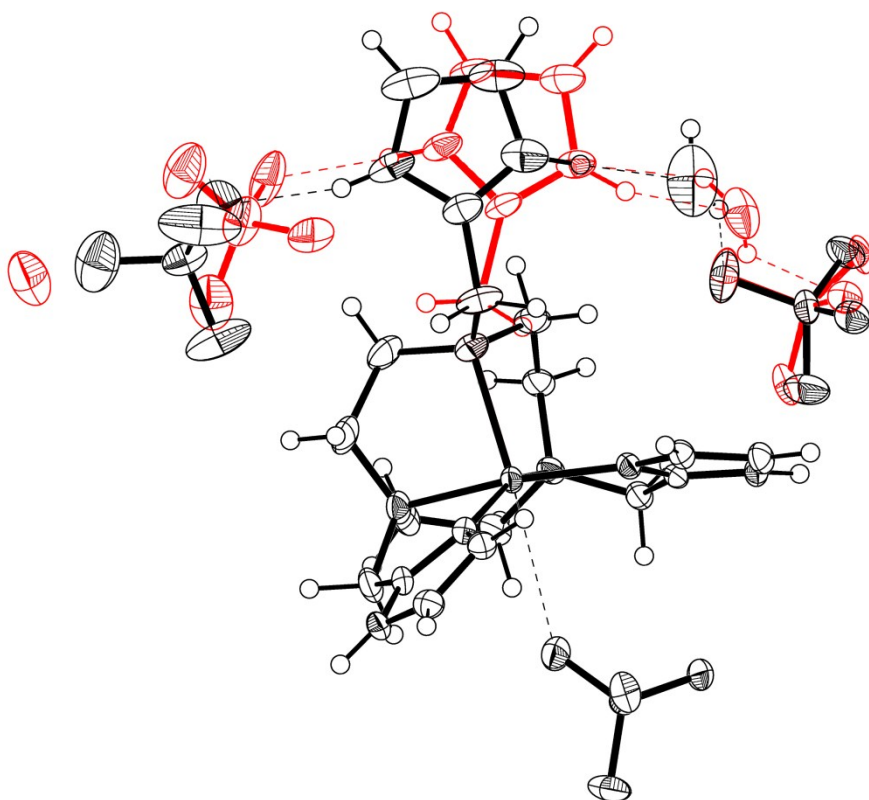


Fig. S 1: Disorder and hydrogen bonding motif in 1. Ellipsoids at 50% probability. Black: 70% occupation, red: 30% occupation. Hydrogens for the 30% occupied second water site could not be assigned. Length of marked Cu-O van-der-Waals contact: 2.924(2) Å (cf. sum of vdW-radii: 292 Å).

Refinement of $[\text{Cu}(\text{NOTI-Me})\text{H}]_2(\text{ClO}_4)_5 \cdot 2\text{TFA} \cdot 4\text{H}_2\text{O}$ (Cu-2)

The asymmetric unit of this structure contains two symmetry-independent complex cations. In one of these cations, copper is additionally coordinated by one water molecule, forming a distorted octahedral coordination geometry. In the other cation, copper is only coordinated by the protonated NOTI-Me ligand with no further contacts shorter than the sum of van-der-Waals radii (distorted tetragonal pyramid). Additionally the asymmetric unit contains three more water molecules, one trifluoroacetic acid molecule with rotational disorder in the CF_3 group ($\sim 80:20$), one trifluoroacetate and five perchlorate anions, one of which is disordered over two orientations ($\sim 80:20$). All moieties but one perchlorate anion are interconnected through a complex hydrogen bonding pattern. The hydrogen positions at the copper-coordinated water molecule, the imidazolium group and the trifluoroacetic acid molecule could be clearly identified by analysis of the difference Fourier map, and were then refined with idealized distances in terms of a riding model (water molecules were refined as rigid bodies). All other hydrogen positions were chosen to form a physical meaningful model, where every hydrogen donor is paired with a suitable acceptor.

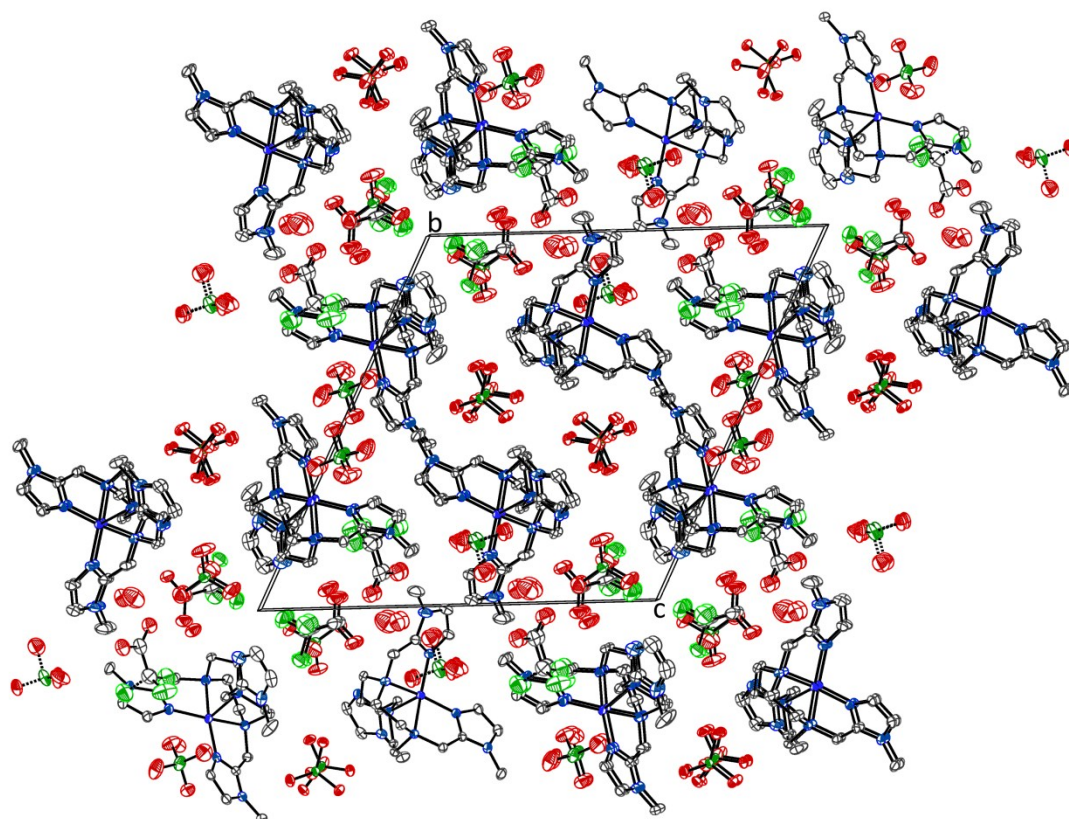


Fig. S 2: Packing motif of 2. Ellipsoids at 50% probability, hydrogen atoms omitted for clarity, CPK color scheme. Disordered moieties are indicated by dashed bonds.

Refinement of [Cu(NOTI-Me)](BF₄)₂ (Cu-3)

The asymmetric unit of this structure contains one third of complex cation, with the central copper atom resting on a 3-fold axis. The triazonane backbone exhibits disorder in two ethylene subunits with a ratio of ~60:40. Both tetrafluoroborate anions also rest on special positions and are disordered: one on a 6₃ axis (disorder about a virtual mirror plane modeled with ~70:30 ratio), the other on the same 3-fold axis as the cation (disorder could only be described by slightly larger thermal displacement parameters). Overall the structure suffers from slightly substandard resolution, but structure proof can still be claimed with confidence. Absolute structure was determined with a Flack x parameter of 0.035(8).

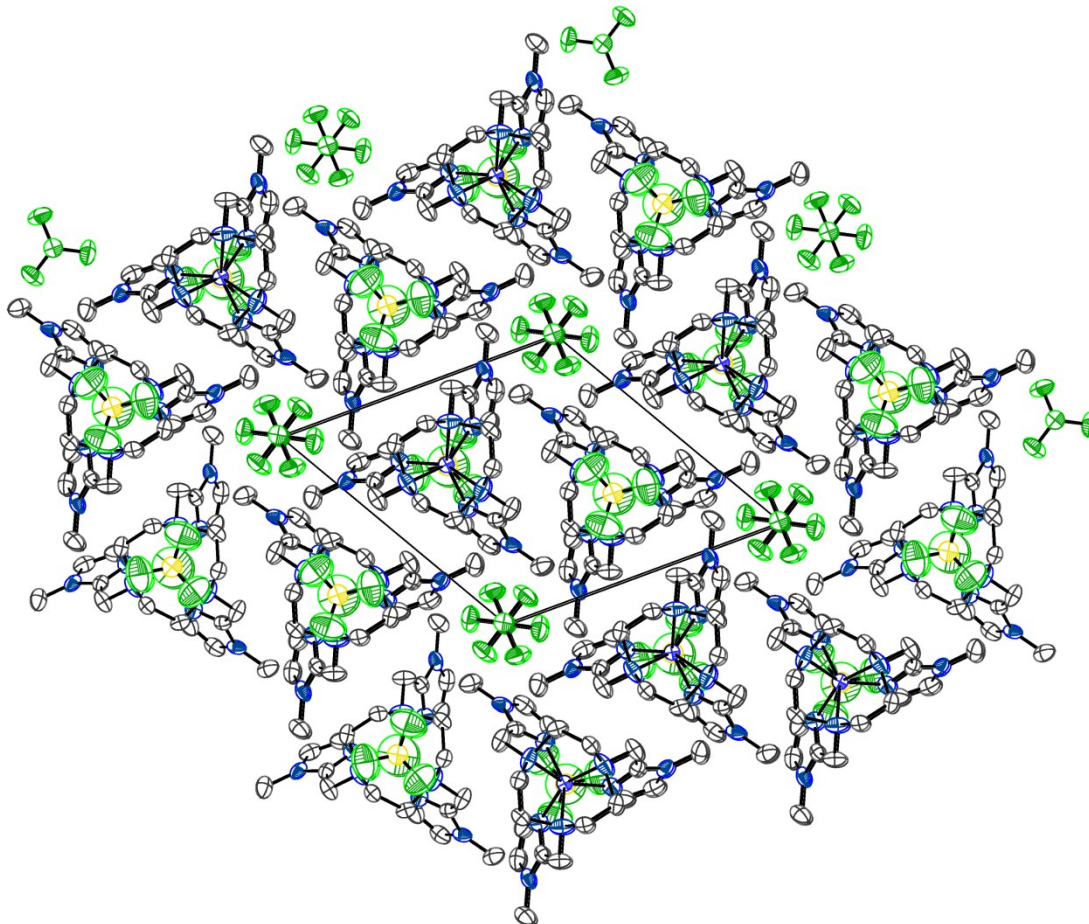


Fig. S 3: Packing motif of 3, top-down view on the a-b plane (along the rotation axes). Ellipsoids at 50% probability, hydrogen atoms and disorder omitted for clarity, CPK color scheme.

Refinement of [Cu(NOTThia)](ClO₄)₂ (Cu-4)

The asymmetric unit of this structure contains two Cu complex cations and four perchlorate anions, one of which is disorder by rotation about one of the Cl-O bonds (~50:50 ratio). The shortest intermolecular contacts are formed between sulphur atoms and oxygen atoms of the anions (2.935 – 3.225 Å).

Refinement of [Cu(NOTThia)](NO₃)₂ (Cu-5)

The asymmetric unit of this structure contains the Cu complex cation and two nitrate anions. The shortest intermolecular contacts are formed between sulphur atoms and oxygen atoms of the anions (2.919 – 3.246 Å).

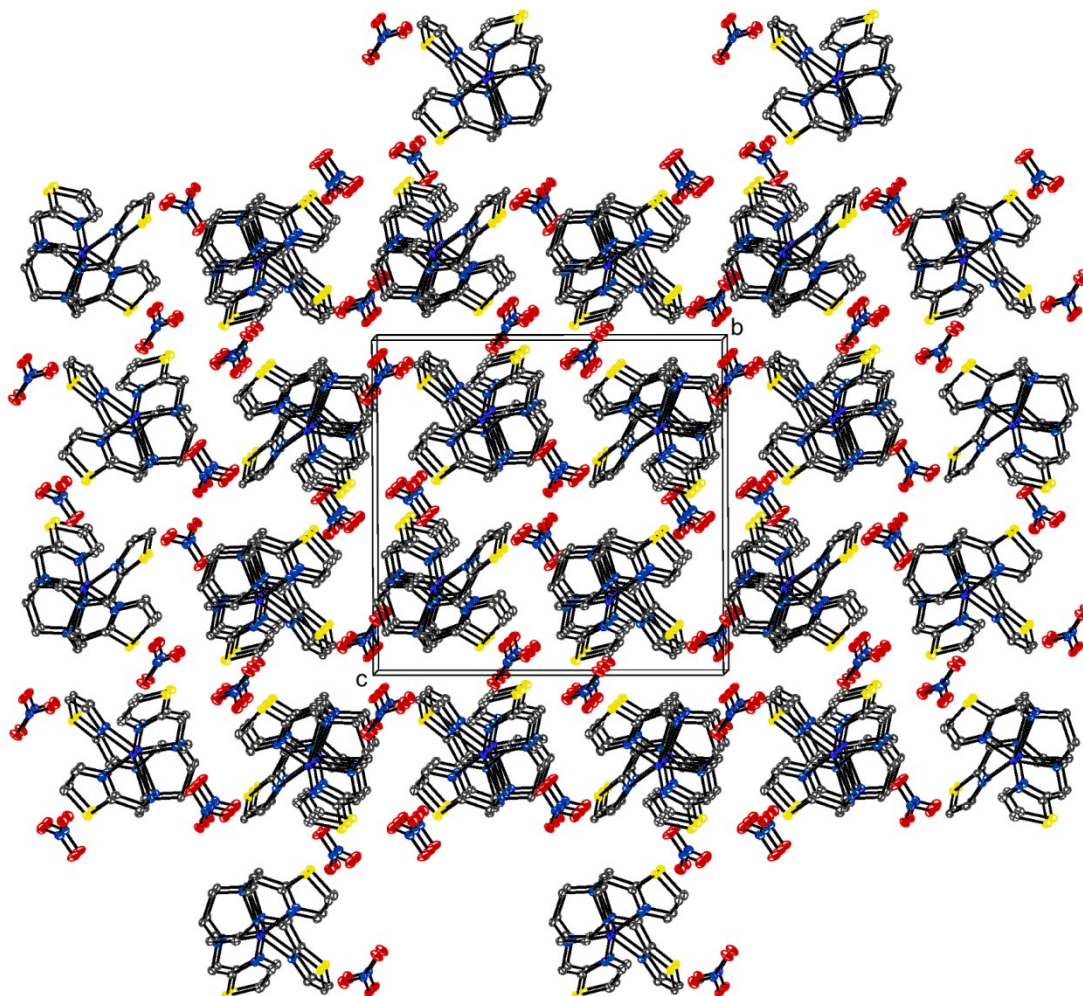


Fig. S 4: Packing motif of 6, top-down view on the b-c plane. Ellipsoids at 50% probability, hydrogen atoms and disorder omitted for clarity, CPK color scheme.