Design and synthesis of a tetrapeptide for removal of lead from water

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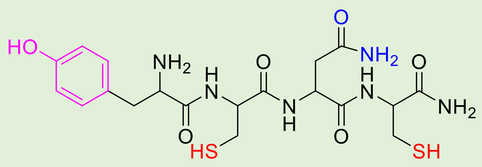
Drinking water contamination via lead pipe corrosion

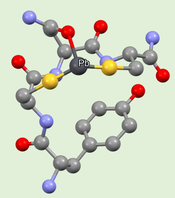
Comparison of new (left), untreated (middle), and orthophosphate treated (right) lead pipes.

Scales from corroded pipes peel off when agitated, causing contamination. While the most notable instance of this is Flint, MI, this is impacting communities across the country.

Lead targeting peptide synthesis and studies



Chemical Formula: $C_{19}H_{28}N_6O_6S_2$
Exact Mass: 500.15118



- YCNC-NH_2 is our target molecule for lead remediation in water
- Peptide structure allows for automated synthesis via SPPS, high water solubility and tunability
- A mixture of hard and soft bases ensures selectivity for lead (II), an intermediate acid
- The phenol on Tyr allows for functionalization to a wide range of surfaces to create a filter
- Computational modeling supports binding

LC-MS reveals synthetic challenges

The synthesis needed overhaul

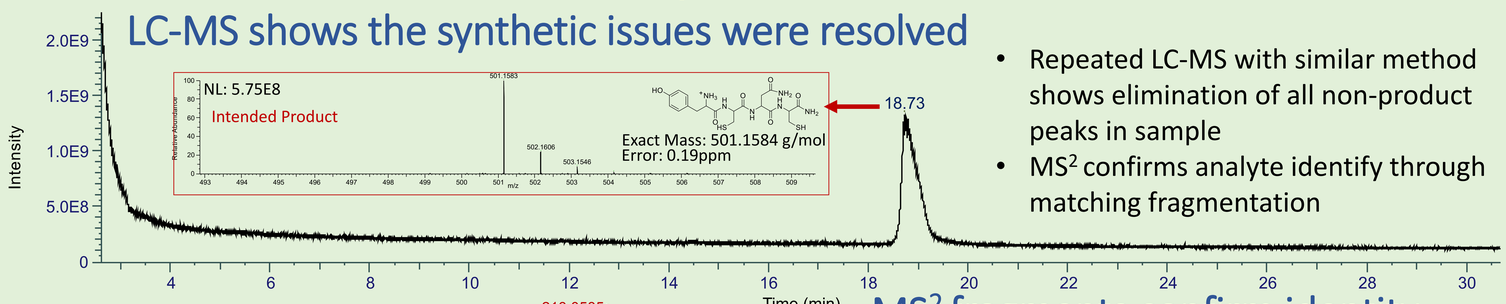
- YCNC-NH_2 is the major product but epimerization is a serious problem
- There may be other byproducts from deletions and truncations
- Can both problems be solved synthetically?

Target Analyte	Peak Area (CPS/min)
YCNC-NH_2	4.09E10
Diastereomer #1	1.59E10
Diastereomer #2	1.76E10
Diastereomer #3	2.87E10
Diastereomer #4	1.67E10

Synthetic overhaul to make a cleaner product

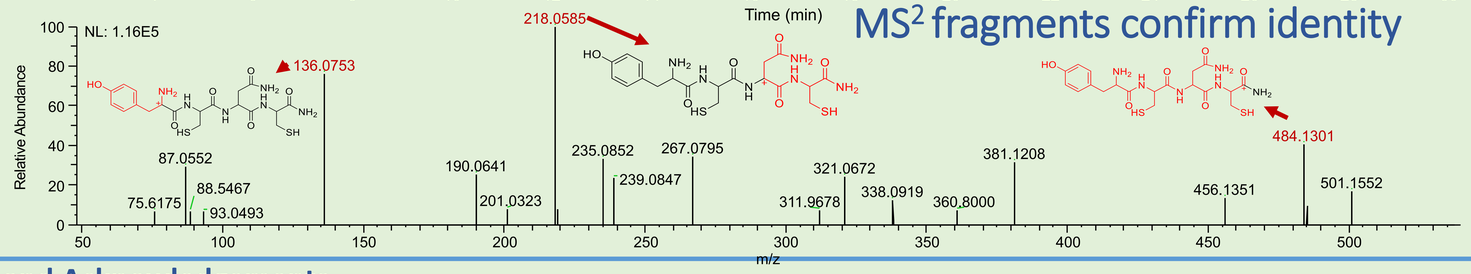
- Coupling agent switched from only HATU to DIC for Cys residues and HATU for the other → DIC shows reduced epimerization for prone residues such as Cys or His
- We reduced the time of deprotections tenfold and the amount of base used → Less overall time exposed to base prevented deprotonation at the α carbon, interrupting epimerization
- The solvent system was changed from 100% DMF to a DCM/DMF mixture → Slows proton transfers during coupling, interrupting epimerization
- Solvent washes lengthened and increased in frequency → Leads to fewer side products as unreacted products are thoroughly removed

LC-MS shows the synthetic issues were resolved



- Repeated LC-MS with similar method shows elimination of all non-product peaks in sample
- MS^2 confirms analyte identify through matching fragmentation

MS^2 fragments confirm identity



Literature

Farkas, E.; Buglyó, P., 8. Lead(II) Complexes of Amino Acids, Peptides, and Other Related Ligands of Biological Interest. In *Lead: Its Effects on Environment and Health*, Astrid, S.; Helmut, S.; Roland, K. O. S., Eds. De Gruyter: Berlin, Boston, 2017; pp 201-240. Vašková, J.; Krempaská, K.; Žatko, D.; Mudroň, P.; Glinská, G.; Vaško, L., Effects of Humic Acids in Chronic Lead Poisoning. *Biological Trace Element Research* **2019,** *187* (1), 230-242. Merrifield, R. B., Solid phase synthesis (Nobel lecture). *Angewandte Chemie International Edition in English* **1985,** *24* (10), 799-810. Lukszo, J.; Patterson, D.; Albericio, F.; Kates, S. A., 3-(1-Piperidinyl)alanine formation during the preparation ofC-terminal cysteine peptides with the Fmoc/t-Bu strategy. *Letters in Peptide Science* **1996,** *3* (3), 157-166.

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