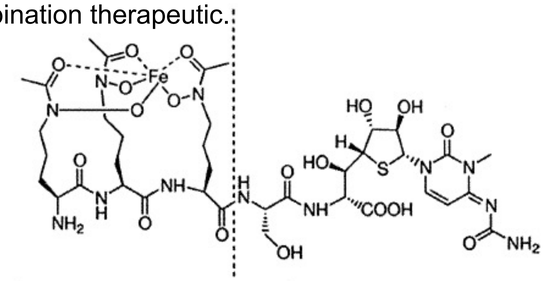
Synthesis of a Novel Antimicrobial Siderophore

Connor Horne[1], Tessa Whitaker[1], Brian Goess[1], Steven Fiester[1]
[1]University of South Carolina School of Medicine Greenville, Greenville, SC
[1]Department of Chemistry, Furman University, Greenville, SC
[2]Department of Pathology, Prisma Health, Greenville, SC

Introduction

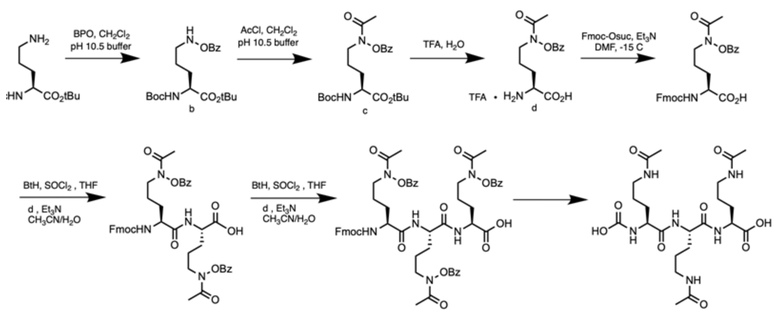
- Antibiotic resistance is an ever-growing threat to healthcare
- Many different techniques are being explored to combat microbes within our bodies that cause human infections.
- Siderophore based iron uptake has shown a plausible therapeutic target and some can be easily synthesized and modified chemically.
- Gallium has been shown to have antimicrobial activity when introduced to microbes.
- Gallium could be incorporated into a siderophore making the siderophore antimicrobial.
- In this project we aim to synthesize a gallium-siderophore linked to a natural antibiotic in order to explore a potential combination therapeutic.



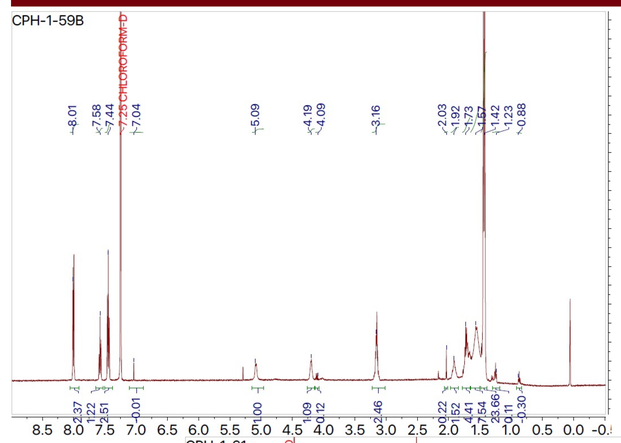
Ferrichrome (hydroxamate siderophore) SB-217452

Methods

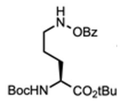
- We followed Lin et al.'s published five step synthesis of a precursor compound to an iron containing siderophore compound, supplemented with Heemstra et al.'s and Katritzky et al.'s published syntheses of a similar molecules in order to create the first half of our compound.

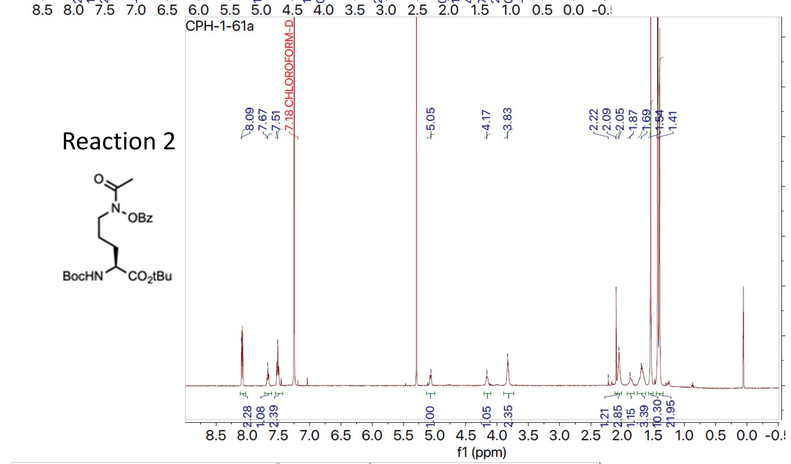


Results

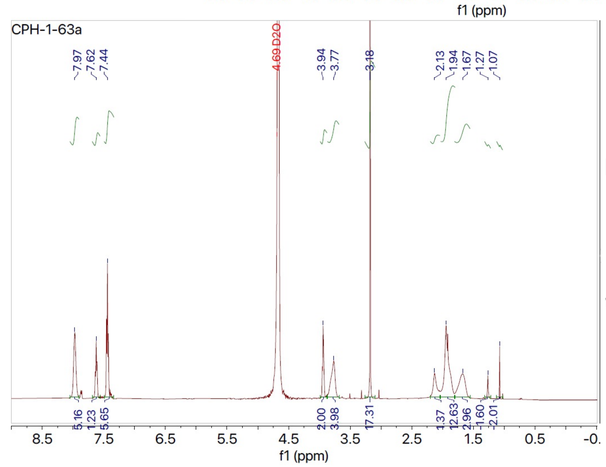


Reaction 1

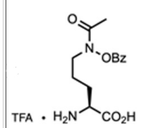


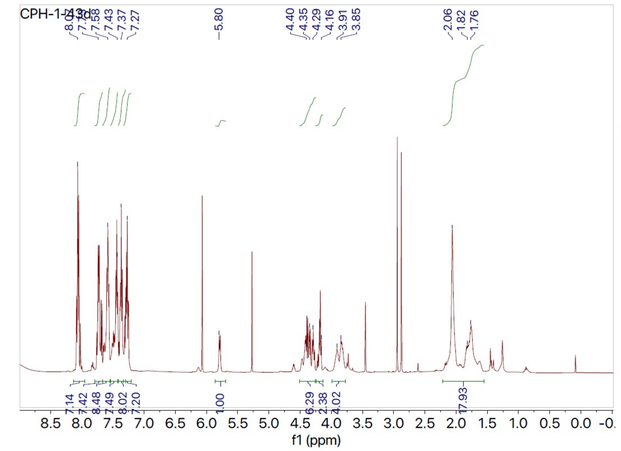


Reaction 2

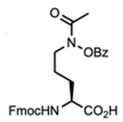


Reaction 3





Reaction 4



Discussion and Future Directions

- The product of step 4, was successfully synthesized and isolated.
- Reactions 5, 6, and 7 are still underway in the Goess laboratory.
- Following complete synthesis,the compound will undergo gallium insertion making the active antimicrobial siderophore.
- The active antimicrobial siderophore will then undergo biological testing in the Fiester Laboratory to better understand its antimicrobial properties.
- If the siderophore is biologically active, the natural antimicrobials will be added to the gallium-siderophore.
- This "two hit" combination drug will then move on to biological testing in the Fiester Laboratory.

References

- Bernstein LR. Mechanisms of therapeutic activity for gallium. Pharmacol Rev. 1998 Dec;50(4):665-82. PMID: 9860806.
- Biometals. 2009 Feb;22(1):3-13. doi: 10.1007/s10534-008-9199-7. Epub 2009 Jan 7. PMID: 19130258; PMCID: PMC2757582.
- Braun V, Pramanik A, Gwinner T, Köberle M, Bohn E. Sideromycins: tools and antibiotics.
- Heemstra JR, Walsh CT, Sattely ES. Enzymatic tailoring of ornithine in the biosynthesis of the Rhizobium cyclic trihydroxamate siderophore vicibactin. J. Am. Chem. Soc. 2009;131:15317–15329. doi: 10.1021/ja9056008. - DOI - PMC - PubMed
- JJ, Rogers HJ, Spalding PB, Ward CG. Iron and infection: the heart of the matter. FEMS Immunol Med Microbiol. 2005 Mar 1;43(3):325-30. doi: 10.1016/j.femsim.2004.11.010. PMID: 15708305.
- Kaneko Y, Thoendel M, Olakanmi O, Britigan BE, Singh PK. The transition metal gallium disrupts Pseudomonas aeruginosa iron metabolism and has antimicrobial and antibiofilm activity. J Clin Invest. 2007 Apr;117(4):877-88. doi: 10.1172/JCI30783. Epub 2007 Mar 15. PMID: 17364024; PMCID: PMC1810576.
- Katritzky AR, Todadze E, Cusido J, Angrish P, Shestopalov AA. Selective peptide chain extension at the N-terminus of aspartic and glutamic acids utilizing 1-(N-protected-alpha-aminoacyl)benzotriazoles. Chem Biol Drug Des. 2006 Jul;68(1):37-41. doi: 10.1111/j.1747-0285.2006.00411.x. PMID: 16923024.
- Lin Z, Xu X, Zhao S, Yang X, Guo J, Zhang Q, Jing C, Chen S, He Y. Total synthesis and antimicrobial evaluation of natural albomycins against clinical pathogens. Nat Commun. 2018 Sep 4;9(1):3445. doi: 10.1038/s41467-018-05821-1. PMID: 30181560; PMCID: PMC6123416.
- Rossolini GM, Arena F, Pecile P, Pollini S. Update on the antibiotic resistance crisis. Curr Opin Pharmacol. 2014 Oct;18:56-60. doi: 10.1016/j.coph.2014.09.006. Epub 2014 Sep 23. PMID: 25254623.

Contact: CPHORNE@Email.SC.edu
C.H. was a UofSC SOMG Summer Research Scholar funded by the Sargent Foundation