Alicia Wagner

Senior

Forensic Science

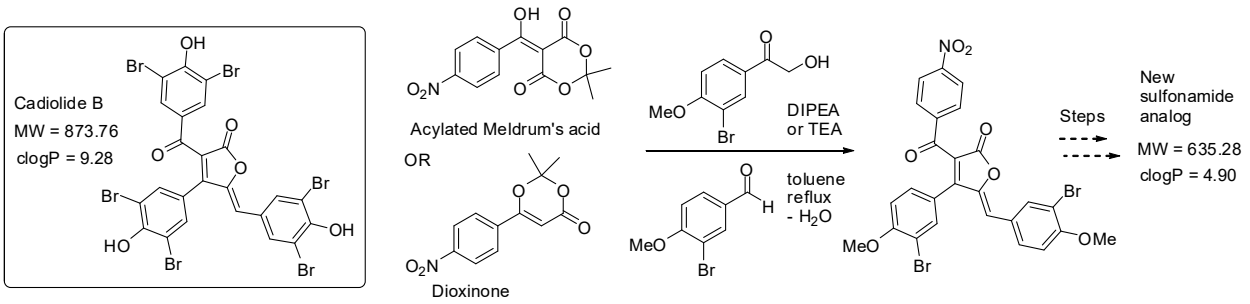
Laboratory Synthesis of Cadiolide Analogs

Mentor: Dr. Pier Cirillo

Cadiolide B is a marine natural product with promising activity against growth of methicillin-resistant *Staphylococcus aureus* (MRSA) (1,2,3), an important pathogen involved in nosocomial infections. A potential problem preventing Cadiolide B from being an orally-bioavailable drug is low solubility due to the presence of multiple lipophilic bromine atoms. Structure-Activity relationship studies by Franck's group (3) have shown that one bromine atom on each of the two Southern rings is sufficient to maintain activity. Moreover, when the Western ring is also replaced with a smaller and un-brominated furan ring, the resulting compound is four fold more potent against bacterial growth than Cadiolide B (3). The goal of this project was to investigate whether it is possible to further enhance the antibiotic potential of the Cadiolides, especially against MRSA. To do so, I designed and generated two sulfonamide-containing analogs that are expected to lower the water-octanol partition coefficient (logP) of the molecule, and hence improve its absorption. Future work will involve biological testing of these compounds to determine the antibacterial potency against MRSA.

The multi-step synthetic approach to these cadiolide analogs hinged on generating an aniline-containing advanced intermediate, which could be converted in the last step into a wide variety of solubilizing polar functionalities such as amides, carbamates, sulfonamides, ureas, or amino-glycosides, by using standard methods and commercially available reagents. The aniline group could be carried through the earlier steps of the synthesis masked as a nitro group, only to be revealed in the second-last step. Thus, Meldrum's acid was acylated with para-nitro-benzoyl chloride, then made to undergo a three-component coupling to form the acylfuranone ring with mono-brominated ketone and aldehyde according to Franck's method(4). The methyl ethers were then cleaved to reveal the hydroxyl groups, and reduction of the nitro group to aniline produced the desired advanced intermediate. The targeted amount for each synthesized analog was 50 mg at 98% purity, such that there is enough sample for final purification, characterization, and biological testing.

Four compounds were successfully synthesized: the nitro- and the aniline advanced intermediates, and the methyl-, and ethyl sulfonamide analogs. Unfortunately, low yields became a prominent issue in the latter steps of the synthesis, preventing us from reaching the desired amounts of final compounds. The focus for future research will be scaling up or looking for an alternative synthesis to produce more of the aniline intermediate(5), and eventually, more analogs. During this process, we also investigated whether the use of a dioxinone or an acylated Meldrum's acid adduct is more efficient to make the acylfuranones. The approach involving Meldrum's acid has lower yields and reproducibility issues, but it is much more time-efficient. The dioxinone approach yields a higher quality intermediate, in greater amounts, but is much more time consuming. Future research will attempt to optimize the Meldrum's acid approach in order to increase yields and product quality.



References

(1) Wang, Weihong, *et al*. (2010). "Antibacterial Butenolides from the Korean Tunicate Pseudodistoma antinboja." *Journal of Natural Products,* (Vol. 75), 2049-2054.

(2) van Hal, Sebastiaan J., & Fowler Jr, Vance G. (2013). "Is It Time to Replace Vancomycin in the Treatment of Methicillin-Resistant Staphylococcus aureus Infections?" *Clinical Practice*, (Vol. 56), 1779-1788.

(3) Boulange, Agathe, *et al.* (2015) "Synthesis and Antibacterial Activities of Cadiolides A, B, and C and analogues" *Biorganic & Medicinal Chemistry* 23 (13): 3618-3628.

(4) Peixoto *et al.* (2013). "Versatile Synthesis of Acylfuranones by Reaction of Acylketenes with α-Hydroxyl Ketones: Application to the One-Step Multicomponent Synthesis of Cadiolide B and Its Analogues". *Eur. J. Org. Chem. 16:* 3316-3327.

(5) For alternative syntheses see: (a) Boukouvalas, John and Thibault, Charles. (2014) "Step-Economical Synthesis of the Marine Ascidian - Antibiotics Cadiolide A, B, and D" *Journal of Organic Chemistry*. (Vol. 80) 681-684. (b) Heung, Kang; Wai, Joong; Kim, Hong; Young, Hee; Gendragiri, Wattut PCT Int. Appl. (2014), WO 2014027826 A1; Priority date 2012-08-13.