

Title: Synthesis of α-acylamino and α-acyloxy amide derivatives of desmycosin and evaluation of their antibacterial activities

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Bacterial resistance to the existing drugs requires a constant development of new antibiotics. Especially compounds active against gram-negative bacteria are difficult to target. Most effective in terms of time, effort and success rate is the medicinal chemistry driven development (evolution) based on existing antibiotics. Towards this end, macrolide antibiotics were modified to give new derivatives, aiming for enhanced antibacterial activities and physicochemical profiles. This work describes the structural diversification at the C-20 aldehyde moiety of desmycosin into α-acylamino and α-acyloxy amide functionalities in a very efficient and simple way, using isonitrile mediated multi component reactions. The desired compounds were obtained in 45–93% yield under mild conditions. Antibacterial activities were determined against gram-negative Allivibrio fischeri. The test revealed that the activity is highly dependent on the amine component introduced. Thus, methylamine derived desmycosin bis-amide displayed an enhanced inhibition rate vs. desmycosin (99% vs. 83% at 1 μM). In Ugi reaction, amine and isocyanide components with longer acyclic or bulky substituents reduced potency. In contrast, the carboxylic acids with increased chain length substituents afforded conjugates with increased bioactivity. In Passerini (P-3C) reaction, butyric acid derived α-acyloxy amide showed much better result displaying higher activity (90% at 1 μM) than the reference desmycosin.

Biography

T. Budragchaa has completed her PhD at the University of Vienna, Austria concentrating in asymmetric synthesis and application of bronsted acid catalysis and their applications. Currently, she is doing her postdoctoral research at the Department of Bioorganic Chemistry, Leibniz Institute of Plant Biochemistry, Halle Saale. She focuses on modification of exisiting macrolide moieties to enhanced antibacterial activities and finetune the physicochemical profiles as well as modification of plant derived bioactive compounds

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Session name/ number: Medicinal Chemistry
Category: (Oral presentation/ Poster presentation): Poster presentation