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Discovery and development of diterpene-based inhibitors of ArnT-mediated colistin resistance

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Abstract

Colistin is a last-line antibiotic for the treatment of multidrug resistant Gram-negative bacterial infections. Recently, a natural ent-beyerene diterpene was identified as a promising inhibitor of the enzyme responsible for colistin resistance mediated by lipid A aminoarabinosylation in Gram-negative bacteria, namely ArnT (undecaprenyl phosphate-alpha-4-amino-4-deoxy-l-arabinose arabinosyl transferase). To explore the structure-activity relationship (SAR), semi-synthetic analogs of hit were designed, synthesized, and tested against colistin-resistant Pseudomonas aeruginosa strains, including clinical isolates. Microbiological assays coupled with molecular modeling showed that the ent-beyerane scaffold bearing an oxalate group at C-18/C-19, or a sugar moiety at C-19 to resemble L-Ara4N is a fundamental requirement for a more efficient inhibition of bacterial growth likely resulting from a more efficient inhibition of ArnT activity. The easy accessibility of ent-beyerane scaffold from Stevia rebaudiana secondary metabolites provided an effective tool for the development of promising colistin resistance inhibitors.

Biography

Andrea Calcaterra was born in Rome, Italy, in 1984. He received his master's degree in chemistry in 2009 from Sapienza University of Rome and obtained his PhD degree in Pharmaceutical Sciences in 2012. From 2013 to 2020, he was a postdoctoral fellow at Sapienza University. Since 2020 he is Assistant Professor (Researcher type B) of organic chemistry at Sapienza. He is co-author of 31 publications, 1 book chapter and 2 patents. His research activity is focused on the isolation, total synthesis and biological evaluation of natural products from plants, and on the synthesis and supramolecular chemistry of resorc[4]arenes macrocycles.

Publications

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- A Methanol Extract of Scabiosa atropurpurea Enhances Doxorubicin Cytotoxicity against Resistant Colorectal Cancer Cells In Vitro
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