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RHODOTORULIC ACID ANALOGS USING THE UPTAKE PATHWAY FOR BACTERIAL SIDEROPHORES TO CIRCUMVENT ANTIBIOTIC RESISTANCE

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Antibiotic resistance has become a major health problem. The search for new antibiotic therapies is crucial to counter the bacterial resistance. Fe(III) plays a major role in many metabolic reactions. Thus, this element is an essential nutrient for the survival of micro-organisms. As biological environments are depleted in iron, bacteria have developed several methods to acquire Fe(III). One of these strategies is based on the synthesis of low molecular iron chelators, called siderophores, and recognized by specific receptors found on the bacterial membranes. In the literature, the development of antibiotic therapies using the siderophores way of entry to vectorize antibacterial drugs has received a particular attention. This strategy consists in the formation of a siderophore-antibiotic conjugate recognized and actively transported by bacteria. The main objective of this work was to synthesize rhodotorulic acid (a fungal siderophore recognized by several species of gram negative bacteria such as *E. coli*) and 3, 6-analogues disubstituted by different Fe(III) chelating functions. Different syntheses have been studied: i) stereoselective alkylation of dioxopiperazines carrying chiral inductors and ii) coupling of modified amino acids such as ornithine or glutamic acid. Simultaneously, the synthesis of piperazinic analogues, easier to obtain, has also been studied to help us in the choice of the chelating functions. Tests to evaluate the siderophore-like activity of these analogues have been performed as well as the antibacterial properties of their gallium complexes. Thereafter, analogues may be coupled to antibiotics in order to vectorize drugs and counter the bacterial resistance phenomena.

Recent Publications

1. **Fardeau S, Mullié C, Dassonville-Klimpt A, Audic N, Sasaki A and Sonnet P (2011) Bacterial iron uptake: a promising solution against multidrug resistant bacteria. In "Science against microbial pathogens: communicating current research and technological advances", 2:695-705, Formatex eds, Badajoz, Spain, ISBN 978-84-939843-2-8.**
2. **Antonietti V, Boudesocque S, Dupont L, Farvacques N, Cézard C, Da Nascimento S, Raimbert J F, Socrier L, Robin T J, Morandat S, El Kirat K, Mullié C and Sonnet P (2017) Synthesis, iron(III) complexation properties, molecular dynamics simulations and *P. aeruginosa* siderophore-like activity of two pyoverdine analogs. European Journal of Medicinal Chemistry 137:338-350.**
3. **Fardeau S, Dassonville-Klimpt A, Audic N, Sasaki A, Pillon M, Baudrin E, Mullié C and Sonnet P (2014) Synthesis and antibacterial activity of catecholate-ciprofloxacin conjugates. Bioorganic and Medicinal Chemistry 22(15):4049-4060.**
4. **Dobias J, Dénervaud-Tendon V, Poirel L and Nordmann P (2017) Activity of the novel siderophore cephalosporin cefiderocol against multidrug-resistant gram-negative pathogens. European Journal of Clinical Microbiology & Infectious Diseases doi: 10.1007/s10096-017-3063-z.**

Biography

Catherine Mullié has obtained her PhD in Microbiology and a PharmD at the University of Lille, France, in 1999. After a Post-doc year at the Faculté de Medicine in Amiens (Laboratoire d'Immunologie, INSERM-EMI 0351), she was appointed as Assistant Professor at the Faculté de Pharmacie in Amiens in 2000 and joined the LG-2A in 2008. She has been a member of the French Society for Microbiology since 2000. Her research is focused on the development of new antimicrobial and antimalarial drugs, with a special interest in efflux-mediated antibiotic resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii.* She currently heads the French part of a bilateral project funded by France and Algeria (Partenariat Hubert Curien Tassili) on this topic.

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