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Novel Sortase A inhibitors to counteract gram-positive bacterial biofilms

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Sortase A (SrtA) is a membrane enzyme responsible for the covalent anchoring of surface proteins on the cell wall of Gram-positive bacteria. Nowadays it is considered an interesting target for the development of new anti-infective drugs which aim to interfere with important Gram-positive virulence mechanisms. Along the years, we studied the anti-staphylococcal and anti-biofilm activity of some natural and synthetic polyhalogenated pyrrolic compounds, called pyrrolomycins. Some of them were active on Gram-positive pathogens at a μg/mL range of concentration (1.5-0.045 μg/mL) and showed a biofilm inhibition in the range of 50-80%. In light of these encouraging results, herein we present our efforts in the design and synthesis of novel pyrrolomycins. To dispose of sufficient amount for the in-depth *in vitro* investigation, we developed an efficient and easy-to-use microwave synthetic methodology. All compounds showed a good inhibitory activity toward SrtA, in accordance with the molecular modelling studies, having IC_{50} values ranging from 130 to 300 μM comparable to berberine hydrochloride, our reference compound. Particularly, the pentabromo-derivative exhibited the highest capability to interfere with biofilm formation of *S. aureus* with an IC_{50} of 3.4 nM. This compound was also effective in altering *S. aureus* murein hydrolase activity, responsible for degradation, turnover, and maturation of bacterial peptidoglycan and involved in the initial stages of *S. aureus* biofilm formation.

Biography

Maria Valeria Raimondi has completed her PhD in Pharmaceutical Science at the University of Palermo, Italy and Post-graduated Master in Drug Design and Development at University of Pavia, Italy. She has worked as a Visiting Scientist in Medicinal Chemistry at University of Hamburg-Fakultät MIN-Fachbereich Chemie-Organische Chemie. She works as an Assistant Professor in Medicinal Chemistry at University of Palermo, Italy. She is a Lab Chief for Laboratory of Synthesis of Heterocyclic Compounds with Potential Biological Activity at University of Palermo, Italy, Department of Biological, Chemical and Pharmaceutical Sciences and Technologies. She has published more than 40 papers in international peer-reviewed journals.

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