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# AlkylGuanidino Ureas, From a Serendipitous Discovery to a Ra-Tional Design: Molecular Simplification Approach and Mem-Brane-Based MoA Investigation †

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Nowadays, the rise of bacterial resistance gets on the podium in the race among the most worrisome Public Health issues. Currently available antibiotics are becoming ineffective to treat infectious diseases, prompting a challenging development of new antibiotics with innovative chemical scaffolds and Modes of Action (MoAs).

We recently reported the serendipitous discovery of the class of the AlkylGuanidino Ureas (AGUs), amphipathic compounds exerting a potent broad-spectrum bactericidal activity. Briefly, a bis-guanidino amine (**1**, Figure 1) was found to spontaneously generate a multicomponent mixture including oligomers through a hypothesized carbon dioxide capture. A multidisciplinary approach of in-depth MS studies, design, and synthesis led to the identification of a tetrasubstituted guanidino urea (**2**, Figure.1) endowed with Minimal Inhibitory Concentration (MIC) values ranging from 0.5 to 16 μg/mL on both Gram-positive and Gram-negative bacterial species, including antibiotic-resistant clinical isolates. Thus, we designed and synthesized a library of analogues of **2** by modifying the length of the alkyl spacers and the *N*-guanidino substitutions, allowing the collection of interesting preliminary structure-activity relationships (SARs).

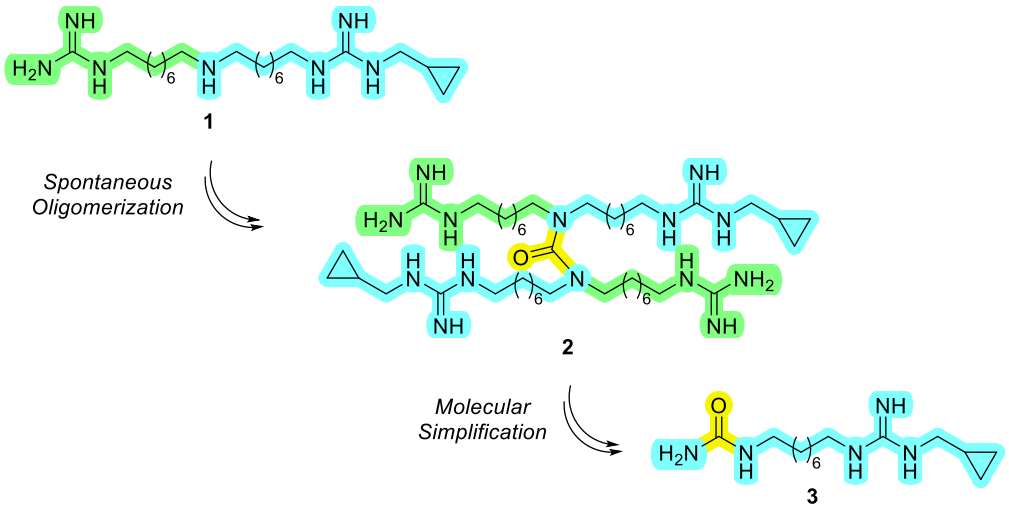


**Figure 1.** Representative compounds of the AGUs class **1–3**.

An insight into the AGUs MoA was reached through a derivatives rational design via a molecular simplification approach and a simplified derivative (**3**, Figure 1) emerged for its antibacterial profile (MICs range 0.5–16 μg/mL). Also, we developed a modified Parallel Artificial Membrane Permeability Assay (PAMPA) by using bacterial phospholipids-endowed bilayers and poorly permeable probes to assess the ability of AGUs to disrupt the bilayers and affect their permeability. Furthermore, molecular dynamics on simulated bacterial bilayers highlighted the strong interaction of AGUs with the membranes in a "carpet-like" manner. However, *in cellulo* assays with propidium iodide and SYTO 9 validated the model-based experiments and confirmed the AGUs membrane-active MoA. In summary, the AGUs class is proven to be worthy of interest in the Med Chem frame for its innovative chemical structure and potent antibacterial activity, with no evidence of detrimental effects.