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Pilicides inhibit the FGL chaperone/usher assisted biogenesis of the Dr fimbrial polyadhesin from uropathogenic *Escherichia coli*

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Abstract

Background: The global spread of bacterial resistance has given rise to a growing interest in new anti-bacterial agents with a new strategy of action. Pilicides are derivatives of ring-fused 2-pyridones which block the formation of the pili/fimbriae crucial to bacterial pathogenesis. They impair by means of a chaperone-usher pathway conserved in the Gram-negative bacteria of adhesive structures biogenesis. Pili/fimbriae of this type belong to two subfamilies, FGS and FGL, which differ in the details of their assembly mechanism. The data published to date have shown that pilicides inhibit biogenesis of type 1 and P pili of the FGS type which are encoded by uropathogenic *E. coli* strains.

Results: We evaluated the anti-bacterial activity of literature pilicides as blockers of the assembly of a model example of FGL-type adhesive structures, – the Dr fimbriae encoded by a *dra* gene cluster of uropathogenic *Escherichia coli* strains. In comparison to the strain grown without pilicide, the Dr^+ bacteria cultivated in the presence of the 3.5 mM concentration of pilicides resulted in a reduction of 75 to 87% in the adherence properties to CHO cells expressing Dr fimbrial DAF receptor protein. Using quantitative assays, we determined the amount of Dr fimbriae in the bacteria cultivated in the presence of 3.5 mM of pilicides to be reduced by 75 to 81%. The inhibition effect of pilicides is concentration dependent, which is a crucial property for their use as potential anti-bacterial agents. The data presented in this article indicate that pilicides in mM concentration effectively inhibit the adherence of Dr^+ bacteria to the host cells, – the crucial, initial step in bacterial pathogenesis.

Conclusions: Structural analysis of the DraB chaperone clearly showed it to be a model of the FGL subfamily of chaperones. This permits us to conclude that analyzed pilicides in mM concentration are effective inhibitors of the assembly of adhesins belonging to the Dr family, and more speculatively, of other FGL-type adhesive organelles. The presented data and those published so far permit to speculate that based on the conservation of chaperone-usher pathway in Gram-negative bacteria , the pilicides are potential anti-bacterial agents with activity against numerous pathogens, the virulence of which is dependent on the adhesive structures of the chaperone-usher type.

Background

Bacterial pathogenesis is a complex process which has been well studied in the case of urinary tract infections (UTIs) mediated by uropathogenic *Escherichia coli* (UPEC) expressing type 1 and P pili. The crucial steps of this mechanism, namely, initial bacterial attachment, invasion and biofilm formation, are strictly dependent on the pili function [1,2]. These structures belong to the family of adhesive organelles assembled in accordance with the classical chaperone-usher pathway, which is highly conserved in Gram-negative bacteria. Pili, fimbriae or amorphic adhesive oganelles are linear homo- or heteropolymers of hundreds to thousands of protein subunits. All these proteins possess a conserved immunoglobuline-like structure denoted by the lack of the seventh β-strand, G. The effect of this structural defect is a hydrophobic acceptor cleft flanked by the β-strands A and F [3-6]. The folding of

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