The total synthesis of albicidin and the synthesis of derivatives to elaborate structure activity relationships

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Abstract

Xanthomonas albilineans belongs to the group of Gram-negative, aerobic bacteria that produce an antibiotic termed albicidin, which was described in 1983 for the first time. The structure elucidation took nearly 30 years and revealed a polypeptide containing several non-proteinogenic aromatic amino acids. Albicidin contains a cinnamic acid derivative, which is additionally substituted with a methyl group at the Michael system and a hydroxy group in *para* position of the aromatic ring. Besides *para* amino benzoic acid it also contains structurally related amino acids and one β-cyanoalanine, which is the only α-amino acid of albicidin. It shows a unique mode of action of bacterial DNA-gyrase inhibition. Combining the unprecedented structure of albicidin with its potency as an antibiotic, albicidin might be developed as a new lead structure and thereby generating a new class of antibiotics.

This thesis describes the first total synthesis of albicin applying a convergent synthetic approach. It includes the elaboration of a protecting group strategy, the synthesis of unusual building blocks and the optimization of peptide coupling conditions. With this synthetic protocol it is possible to obtain high amounts of this interesting natural product for the first time and to investigate its biological and physicochemical properties. Furthermore the stereochemistry of the natural product could be determined by the synthesis of both enantiomers of albicidin. The synthetic protocol was further applied to obtain a variety of different derivatives of albicidin. Assessment of the antibacterial activity of those compounds revealed a relation between the chemical structure and the biological activity. The so called structure activity relationships enable to design biological active derivatives with possibly improved pharmacological properties. Additionally the mechanism of resistance against albicidin by a protease named AlbD, produced by *Pantoea dispersa*, was investigated. In the course of these studies the minimal motive of this detoxifying enzyme was determined and AlbD was further characterized. These results enable the directed synthesis of derivatives to overcome the above described mechanism of resistance against albicidin.