Novel chitinase inhibitors, Argifin and Argadin; Solid phase total synthesis and creation of potent derivatives using rational molecular design

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Chitinases that hydrolyze β-(1,4)-linked *N*-acetylglucosamine have been proposed as attractive targets for the development of compounds to control pests, disease vectors and for drugs against a range of human pathogens. Since chitin is a major structural component of fungi and insects, with 18 chitinases playing important physiological roles in these organisms, chitinase inhibitors are of considerable interest as potential fungicides and insecticides. They also offer significant potential for treatment of asthma and other diseases in humans.

During screening for chitinase inhibitors, we isolated two new cyclic pentapeptides, named Argifin and Argadin, from the cultured broths of *Gliocladium* sp. FTD-0668 and *Clonostachys* sp. FO-7314, respectively. The structures of Argifin and Argadin were elucidated by amino acid analysis and NMR experiments. Additionally, three-dimensional structures of Argifin and Argadin, in complex with *Serratia marcescens* chitinase B (*Sm*ChiB), were resolved by X-ray crystallography, resulting in detailed visualization of the interaction of Argifin and Argadin with *Sm*ChiB. This produced opportunities for structure-based design and synthesis of derivatives, which allows the creation of a range of more potent compounds.

Computer-aided molecular design facilitates production of analogues which exhibit better activity against *Sm*ChiB. Our research has thus focused on developing efficient synthetic routes for both Argifin and Argadin, as well as for the development of more potent chitinase inhibitors. In this symposium, we report our efficient solid phase total syntheses of Argifin and Argadin, as well as the synthesis of more potent inhibitors based on these two natural products.