Synthesis of Small Molecules Targeting ADP-Ribosyltransferases and Total Synthesis of Resveratrol Based Natural Products

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Akademisk avhandling

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Abstract

Diphtheria Toxin-like ADP-Ribosyltransferases

The Human ADP-ribosyl transferases (ARTDs) are a group of poorly studied enzymes which are believed to be involved in *e.g.* DNA repair, protein degradation, transcription regulation and cell death. Medicinal chemistry programmes aimed at developing selective inhibitors of these ARTDs were initiated. A suitable starting compound for one of these enzymes, ARTD3, was found by screening a library of NAD-mimics using a thermal shift assay. A virtual screening protocol was instead developed in order to find novel inhibitors of ARTD7, 8, and 10. The hit compounds were then further developed into selective inhibitors of the corresponding ARTDs by systematically varying different structural features using a combination of synthetic organic chemistry, computational chemistry and structural biology. Compounds were initially characterized using differential scanning fluorimetry which was later replaced with an enzymatic assay to obtain IC_{50} values. Biotinylated analogs were also synthesized in an attempt to develop an AlphaScreen assay. A selective ARTD3 inhibitor was ultimately identified and found to delay DNA repair in cells after γ-irradiation. These compounds are potentially valuable tools for elucidating the biological role of the poorly characterized ARTD-family of proteins.

Total Synthesis of Resveratrol Based Natural Products

The polyphenolic natural product (-)-hopeaphenol was found to inhibit the type III secretion system present in certain gram-negative bacteria. (-)-Hopeaphenol is a tetramer of resveratrol and in order to investigate whether the entire structure was essential for inhibition two resveratrol dimers, ε-viniferin and ampelopsin B, were synthesized using a flexible and divergent synthetic route. Highlights of the synthetic strategy include the use of cyclopropylmethyl protecting groups, allowing an acid mediated three-step-one-pot deprotection-epimerization-cyclization of an advanced intermediate to form ampelopsin B. All previously reported syntheses of these two natural products include a dimerization of resveratrol which severly limits the possibilities to synthesize structural analogs. This new strategy enables the synthesis of a wide variety of analogs to ε-viniferin and ampelopsin B.

Keywords
organic synthesis, quinazolinone, ARTD, PARP, total synthesis, polyphenols, bensofuranes

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