Synthesis and structure-activity relationships of novel nikkomycin analogs: Inhibitors of the fungal cell wall biosynthesis enzyme chitin synthase

Jun-ichiro Uda\textsuperscript{1}, Kikoh Obi\textsuperscript{1}, Kazuhiko Iwase\textsuperscript{1}, Osamu Sugimoto\textsuperscript{1}, Hiroyuki Ebisu\textsuperscript{1} and Akira Matsuda\textsuperscript{2}

\textsuperscript{1}Central Research Laboratories, Kyorin Pharmaceutical Co. Ltd., 2399-1, Mitarai, Nogi-machi, Tochigi-ken 329-0114, Japan and \textsuperscript{2}Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, Hokkaido 060-0812, Japan

ABSTRACT

A series of novel nikkomycin analogs, which inhibited chitin synthase, the fungal cell wall biosynthesis enzyme, has been synthesized and evaluated their inhibitory activities.

INTRODUCTION

Recently, opportunistic infections caused by various pathogen fungi have been increased and become a critical point of chemotherapy. The some reasons of critical point are increasing resistance of fungi against antifungal drugs and toxicity of antifungal drugs\textsuperscript{1}. From these point into account, it is clear that requirement of new antifungal agents with different targets are highly selective for the fungus\textsuperscript{2}.

On the other hand, the component of fungal cell wall is chitin unit, which is biosynthesized from uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) by chitin synthase (Chs). Natural peptidyl nucleoside nikkomycin Z (NZ: 1), a well known Chs inhibitor act as competitive inhibitors, may be due to their structural similarity to the UDP-GlcNAc (2), substrate for Chs\textsuperscript{3} (Fig.).

In this context, we designed and synthesized a novel series of NZ (1) analogs with enhanced Chs inhibitory activity. Herein, we report the design, synthesis, and biological activity of a novel NZ analogs.

RESULTS AND DISCUSSION

The synthesis of novel NZ derivatives was outlined in Scheme.

Uracil polyoxcin C (UPOC: 3)\textsuperscript{4} as a starting material in the synthesis of novel NZ derivatives. The 5'-amino group of UPOC (3) was acylated with variety N-tert-butoxycarbonyl protected amino acid derivatives (4) in the presence of N-hydroxysuccinimide/DCC to furnish protected NZ derivatives (5). Finally, the protecting groups of 5 was removed with TFA, and the resulting TFA salt of 6 was subjected to ion-exchange resin. After lyophylization of the products, white–pale yellow powder of 6 was obtained.

The newly synthesized NZ analogs were evaluated for \textit{in vitro} anti-Chs activity (the inhibition rate (%) of Chs[isolated from \textit{Candida albicans}] at concentration of 100\mu g/mL and IC\textsubscript{50} values).

Initially, we prepared several simple analogs with a L-cysteine and L-serine residue. Among of them, 6a was indicate most potent anti-Chs activity in this series. Further chemical modification of 6a as a basic structure was carried out as follows; introduction of hydroxyl group of phenyl moiety of 6a and introduction of dimethyl group of \beta-position in terminal amino acid of 6a were enhanced anti-Chs activity.

According to conformational analysis, 6a-c were slightly deviate from NZ because bond length of terminal amino acid were longer than NZ. Therefore, we designed that
the aryl group was directly attached end of L-cysteine which is same bond length as NZ. Unfortunately, in spite of the 6d was well superimpose to NZ, its anti-Chs activity was reduced.

To find out an active compounds with high anti Chs activity, the imaginary receptor-mapping study (IRM study) was a most effective method among other approaches.

From IRM study, we found a hydrophobic region around the β-methyl group in the terminal amino acid. Therefore, we synthesized a series of hydrophobic amino acids, which were then coupled with UPOC to give 6e-g. As expected, newly designed hydrophobic compounds showed potent anti-Chs activity. Especially, compound 6g having a phenanthrene group showed the most potent anti-Chs activity in the series, that IC_{50} value is comparable to NZ.

CONCLUSION
We have developed a design and synthesis of novel NZ analogs and discover a phenanthrene derivative which showed most strong anti-Chs activity same as natural NZ.

REFERENCES