Research Overview of the Laboratory of Analytical Bioorganic Chemistry

Tohoku Journal of Agricultural Research
Vol. 57 No. 1-2, November 2006
Printed in Japan

Research Overview of the Laboratory of Analytical Bioorganic Chemistry

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(Received, April 1, 2006)

Summary

The laboratory of analytical bioorganic chemistry drastically changed its research projects in 2005. Some of the recent achievements are described.

Key words: Antibiotics, Drug resistance, Chemical synthesis, Spider wasp, Nitrated nucleic acid

The central theme of research in our laboratory is the development of new biologically active compounds by organic synthesis. As well as using traditional approaches of natural product chemistry, we employ chemical tools and approaches to study problems in biology and biochemistry.

Design and synthesis of novel antibacterial agents effective against vancomycin-resistant bacteria

One long-term project involves the design and synthesis of novel antibiotics.

Peptidoglycan is a crosslinked polymer that surrounds bacterial cell membranes, enabling the cells to withstand osmotic pressure fluctuations. Damage to the peptidoglycan biosynthesis results in bacterial cell death. And it is an important target for broad spectrum antibiotics. Vancomycin, the drug of last resort in the treatment MRSA, also disrupt this process by binding to Lipid II, a key intermediate in peptidoglycan biosynthesis.

Emergence of resistant bacteria against vancomycin (VRE and VRSA), has recently become popular, and there is a serious concern in clinics. In the vancomycin-resistant bacteria, the chemical structure of a peptidoglycan intermediate Lipid II is changed slightly, and the interaction of vancomycin to the modified lipid II is reduced greatly. We have succeeded to recover the lost

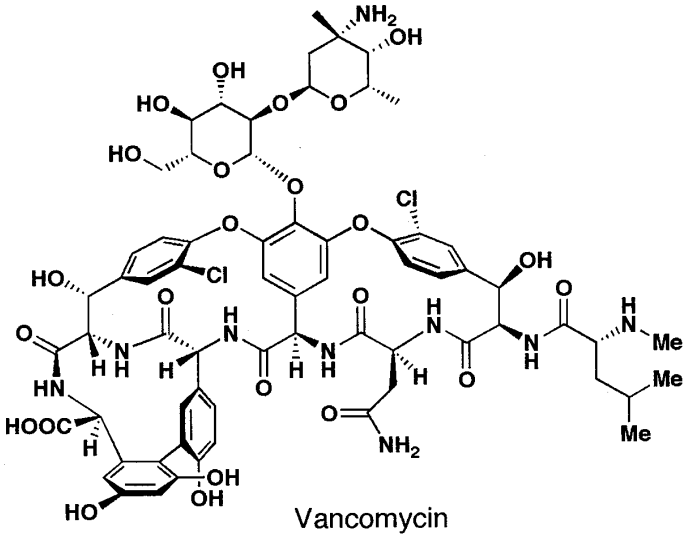

FIG. 1. Chemical structure of the drug of last resort, vancomycin.

antibacterial activities for VRE, by polymerizing vancomycin molecules (Arimoto et al., 1999). In order to develop even more potent antibacterials, we are currently interested in covalently-linked vancomycin dimers. Other groups also reported the excellent antibacterial activities of the dimers against VREs *in vitro*, however, none of these derivatives has been reported to show curative effects *in vivo*. Actually, some of our compounds are quite effective in animal models. The mode of action studies with the vancomycin dimers are underway. In the long run, we are interested in obtaining mechanistic information on individual members of enzyme class involved in the latter stage of peptidoglycan biosynthesis.

Synthesis of structurally complex, biologically active natural products

Complex natural molecules were selected as targets for our current research efforts owing to their biological properties as well as their interesting structures. We place a significant emphasis on synthetic strategies for achieving high levels of stereochemical control in each of these synthesis efforts. Some of these projects involve transannular cycloaddition reactions. For example, we have recently disclosed the asymmetric syntheis of spirotetracyclic carbon core of a marine natural product, mangicol A (Araki et al., 2004). In the synthesis, transannular Diels-Alder (TADA) reaction was employed as a key step. Careful molecular design of a 12-membered ring triene precursor enabled the highly stereoselective construction of three rings in only one synthetic transformation.

Other current synthetic targets involve Pinaic acid (Hayakawa et al., 2003;

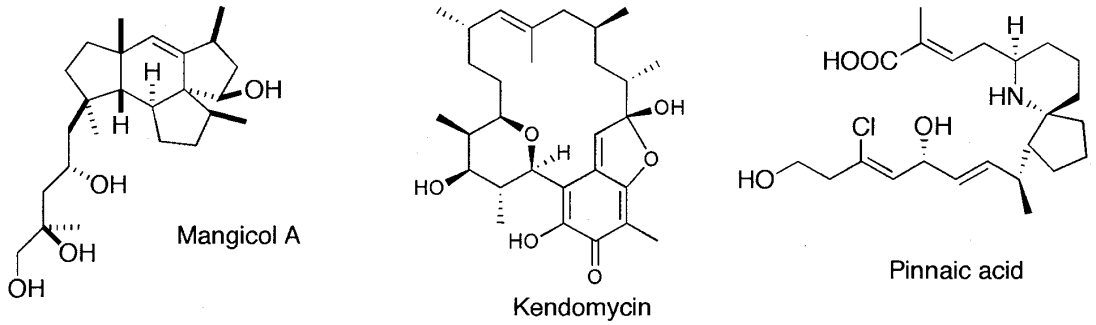

FIG. 2 Some of the synthetic targets in the research group.

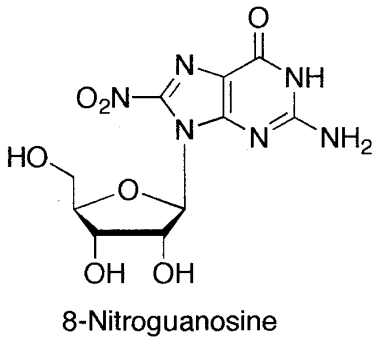

FIG. 3. Chemical structure of nitrated guanosine.

cPLA2 inhibitor), Kendomycin (Sengoku et al., 2004 ; antibiotics), and Nakiterpiosin (cytotoxic).

Chemistry of nitrated nucleic acids

This research is performed in collaboration with Prof. T. Akaike at Kumamoto University. Oxygen radicals such as superoxide anion (O_2^-) and nitric oxide (NO) are produced in the infected body, and play an important role in microbial pathogenesis. Akaike recently found that 8-nitroguanosine was generated from nitration reaction of guanosine via NO formation *in vivo*. The biological function of 8-nitroguanosine, a unique nucleotide derivative, is now focus of great interest in terms of its mutagenic and redox-based signaling potentials. We have been developed the synthetic protocols of this intriguing molecule for the efficient supply. The synthesis also enabled to prepare antibodies with specificities against nitrated nucleic acids.

Characterization of paralytic substance from the venom of spider wasp, *Cyphononyx dorsalis*

This research is performed in collaboration with Prof. D. Uemura at Nagoya University. Wasps of the family of Pompilidae are well known their oviposition behavior. Females of the wasp locate their preys (spiders) and sting them. The stung spiders are soon paralyzed and never walk again. The paralyzed spiders are then carried or dragged to the nest that, in some cases, is prepared before prey capture. Female wasps lay an egg on the body of paralyzed spider. They hatch and the larvae then have live food on which to feed. These intriguing function of solitary wasp venom has attracted a great deal of interest of many scientists.

To date, several neurotoxic components have been characterized from the solitary wasp venom. However, none of these low molecular components were shown to the paralytic activity against their preys.

We collected hundreds of female wasps in Shizuoka prefecture. The venom sac connecting with a sting was carefully squeezed and the venom droplets from stinger. were collected We are now exploring the paralytic components guided by an biological activity assay against spiders.

References

Araki, K., Saito, K., Arimoto, H., Uemura, D., *Angew. Chem., Int. Ed.*, **43**, 81-84 (2004).

Arimoto, H., Nishimura, K., Kinumi, T., Hayakawa, I., Uemura, D., *J. Chem. Soc., Chem. Commun.*, 1361-1362 (1999).

Hayakawa, I., Arimoto, H., Uemura, D., *Heterocycles*, **59**, 441-444 (2003).

Sengoku, T., Arimoto, H., Uemura, D., *Chem. Commun.*, 1220-1221 (2004).