GS04-5 Synthetic study of muraymycins for the development of new antibacterial agents

◯Tetsuya TANINO[1], Satoshi ICHIKAWA[1], Akira MATSUDA[1], Kouichi UOTANI[2]

[1]Faculty of Pharmaceutical Sciences, Hokkaido University, [2]Shionogi & Co., Ltd.

Recently, multi-drug-resistant pathogens against clinically used antibiotics have been widespread. To treat them, it is necessary to develop antibiotics, with a new mechanism of action. Muraymycins (MRYs) are novel nucleoside antibiotics and strong inhibitors of bacterial translocase MraY, which is involved in the intracellular pathway of peptidoglycan biosynthesis. We started the synthetic study of MRYs via total synthesis in order to develop the novel antibacterial agents.

Aiming to the preparation of various MRY analogs, Ugi-four component reaction was used as a key reaction to assemble the framework of MRYs at the late stage of our synthetic approach. After assemblage of the four components, isonitrile, 2,4-dimethoxybenzylamine, isovaleraldehyde and urea-dipeptide carboxylic acid followed by the deprotection, the first total synthesis of MRY D2 has been accomplished. Aithough MRY D2 showed the inhibitory activity against MraY, it did not show any antibacterial activity. In order to enhance the antibacterial activities of MRY D2, the lipophilic MRY derivatives were designed and synthesised. The biological activities of the MRY analogs were tested, and some MRY analogs having the strong antimicrovial activity to multi-drug-resistant pathogens such as MRSA and VRE were found.