PRESS RELEASE

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Tokyo Institute of Technology research: Going with the flow: Facile synthesis of a complex biologically active oligopeptide

Scientists at the Tokyo Institute of Technology utilized micro-flow amide bond formation to achieve total synthesis of the structurally complex, biologically active natural product, feglymycin. The technique they developed allows for efficient preparation of requisite oligopeptides containing highly racemizable amino acids and could directly impact how these agents will be synthesized in the future.

The research community and pharmaceutical industry have had a long-standing interest in developing peptide-based therapeutics owing to their high target specificity, potent activity, and small size relative to protein-based biologics. Towards this end, most peptide-based therapeutics currently available in the market consist of <20 amino acids making them more synthetically accessible and cheaper to manufacture compared to larger protein biologics. However, the preparation of some biologically active oligopeptides is not without its challenges. For example, the vancomycin class of glycopeptide antibiotics, widely used for the treatment of methicillin-resistant *Staphylococcus*, contains an arylglycine moiety, which is prone to undesired racemization during synthetic preparation. More broadly, arylglycines, which most often occur in the form of phenylglycine (Phg), 4-hydroxyphenylglycine (Hpg), and 3,5-dihydroxyphenylglycine (Dpg), are present in a wide array of biologically active natural products, including formadicin, ramoplanin, teicoplanin, and feglymycin. However, despite the extensive representation of this key amino acid in these biologically active molecules, few robust synthetic methodologies for their preparation exist.

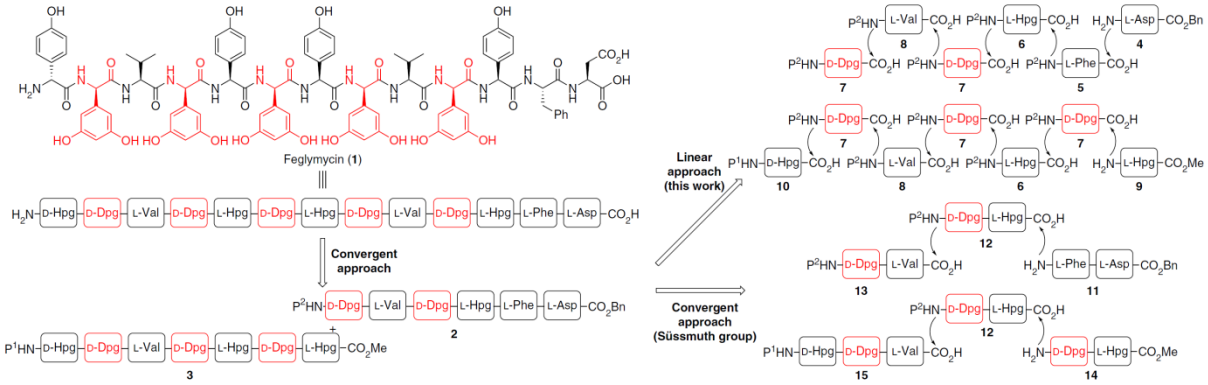

Figure. Comparison of synthetic strategies toward the total synthesis of feglymycin (**1**). Linear/convergent approach highlighted in this work and the convergent approached previously described by Süssmuth in 2009.

To address this challenge, a group of scientists led by Associate Professor Shinichiro Fuse from the Institute of Innovative Research, Tokyo Institute of Technology exploited their lab expertise and previously described micro-flow amide bond formation methodology to tackle this difficult synthetic challenge.

In order to demonstrate the utility of this methodology, they focused on the arylglycine-containing oligopeptide, feglymycin, which possesses a unique helical conformation and potent anti-HIV activity. The first total synthesis of feglymycin was reported in 2009 by Süssmuth and co-workers by using a convergent approach, with 3-(diethyloxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT) mediated amide coupling of the highly racemizable Dpg moieties being a key step. Despite this great achievement, severe racemization was noted when this coupling was attempted with longer peptides, suggesting a linear synthetic approach to feglymycin and related oligopeptides was improbable. Fortunately, Fuse and colleagues successfully implemented the micro-flow amide coupling methodology without severe racemization via the inexpensive and highly atom efficient coupling reagent, triphosgene. Importantly, the linear synthetic strategy highlighted in this research is highly desirable and necessary for the preparation of feglymycin analogs, as it allows the researchers to modify individual components of the molecule. Such precise manipulation of the molecule allows for optimization of the biological activity and physicochemical properties, and is an essential component to any drug discovery/development effort. An additional advantage of this approach is that flow chemistry provides direct access to safe and rapid compound scale-up using continuous operation of the requisite microreactors.

As drug discovery efforts become increasing complex, novel and more efficient methodologies are required to allow rapid preparation and optimization of lead molecules of interest. In the future, this research will undoubtedly pave the way for the synthesis and analog preparation of feglymycin and other biologically active oligopeptides.

Reference

Authors:	Shinichiro Fuse[1], Yuto Mifune[1], Hiroyuki Nakamura[1] and Hiroshi Tanaka[2]
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