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Okayama University

Developing an environmentally friendly mass synthetic method for NEt-3IB candidates for inflammatory bowel diseases

～From the perspective of contributing to SDGs by reducing the volume of waste liquid in synthesizing drug substances～

◆Abstract

- Inflammatory bowel disease (IBD) is a disease associated with diarrhea, bloody stools, and abdominal pain due to chronic inflammation.
- A new small-molecule drug that can be orally administered at a low cost as a treatment for IBDs is also being sought from SDGs perspective of "healthy and well-being for all."
- In this study, we succeeded in developing a large-scale synthetic method that can provide a large and stable supply of NEt-3IB candidates for the treatment of small-molecule IBDs originating from Okayama University, and this result is expected to facilitate the development of NEt-3IB pharmaceuticals.
- Compared with conventional methods, we successfully developed a method for mass-synthesizing environmentally friendly NEt-3IB that improved E-factor, an indicator of environmental burden in multistage drug substance synthesis, by more than 35-fold.
- This approach is expected to be widely applied to the development of large-scale synthetic methods for APIs with low environmental impact.

Professor Hiroki Kakuta and colleagues at Okayama University Graduate School of Medicine and Dental Medicine have succeeded in developing an environmentally friendly mass synthesis method for candidate compounds for the treatment of inflammatory bowel disease under development in cooperation with AIBIOS K.K.. Inflammatory bowel disease (IBD) is a disease associated with diarrhea, bloody stools, and abdominal pain due to chronic inflammation. Antibody drugs have recently been marketed as therapeutic agents, but the increasing cost of medical care and the severity of antibodies to antibody drugs are becoming a problem. Given the disparities in medical care and the tightness of medical practice due to poor populations, new drugs of small molecule type that can be administered orally at low price are being sought. The agonist NEt-3IB of retinoid X receptors (RXRs, Note 1), which we have previously found, has been shown to induce mucosal healing, which has been considered as a therapeutic endpoint for IBD, in addition to its anti-inflammatory effects in models of inflammatory bowel disease. Therefore, it is attracting attention as a potential new small-molecule therapeutic agent for inflammatory bowel disease. Against this backdrop, NEt-3IB is currently developing drugs to treat inflammatory bowel diseases in collaboration with Keio University and AIBIOS K.K.. In this study, we developed a mass synthetic method that is expected to contribute to SDGs by reducing the volume of waste liquid, which is considered to be an organic synthetic problem, for NEt-3IB, which is a drug candidate for the treatment of inflammatory bowel diseases.

Based on the existing synthetic methods, the organic solvents used were converted into fat-soluble ethers (Note 2), which can be recovered and reused. This enables the use of two organic solvents and drastically reduces the volume of liquid waste. This improved E-factor, an indicator of environmentally friendly synthetic methods, by more than 35-fold.

The results of this study will be published on February 1 in the Journal of the Japanese Pharmaceutical Society, *"Chemical and Pharmaceutical Bulletin"*, after being selected for Highlighted paper selected by Editor-in-Chief.

■Publication

＜NEt-3IB being developed as novel candidates for the treatment of small-molecule forms of inflammatory bowel diseases＞

Inflammatory bowel disease is a disease with symptoms such as chronic diarrhea, bloody stools, and abdominal pain, for which the number of patients is increasing worldwide.

Currently, treatment is directed at reducing inflammation with steroids and antibody drugs, followed by a treatment endpoint of mucosal healing, which is maintenance of remission.

However, delayed healing with steroids, high medical costs due to antibody drugs, and serious problems due to the development of antibodies to antibody drugs have been considered.

From SDGs's perspective of "3 Wellbeing and Wellbeing for All," treatment with antibody-based drugs alone can lead to not only poor wealth differences but also healthcare disparities associated with the size of healthcare facilities in developed and developing countries, as well as tightness in healthcare settings.

This makes it noteworthy that small-molecule drugs for inflammatory bowel disease that can be administered orally at a low cost.

In addition to the anti-inflammatory effects of RXR agonists, we noticed that the RXR agonist NEt-3IB created in this study efficiently transferred to the large intestine after medication, and we were interested in its therapeutic efficacy against inflammatory bowel diseases.

NEt-3IB has been found to induce mucosal healing in addition to its anti-inflammatory efficacy, as assessed in mice models of inflammatory bowel diseases.

Against this backdrop, we are collaborating with AIBIOS K.K. to develop NEt-3IB as a new small-molecule anti-inflammatory bowel disease agent that replaces conventional drugs.

＜Research Finding＞

As mentioned above, NEt-3IB has been focused on as a new candidate drug for the treatment of inflammatory bowel diseases, but existing synthetic methods have not been amenable to large-scale supplies due to various complex manipulations, including purifications. In this study, which addressed this issue, we established a stable and large-scale supply-enabled mass synthetic method that is essential for developing NEt-3IB pharmaceuticals. In addition, the use of fat-soluble ethers, which can be recovered and reused and have attracted attention as environmentally friendly organic solvents, has led to a significant reduction in the volume of effluent that is a problem in organic chemistry. The only organic solvents used in all seven processes were fat-soluble ethers and ethanol. Purification by recrystallization alone established a synthetic method capable of supplying large quantities of NEt-3IB with a total yield of more than 30% and a purity of 99%. By reducing the amount of liquid waste and greatly improving the total yield, E-factor, known as an indicator of environmental impact in multi-step synthesis, achieved over 35-fold improvement over the existing synthetic methods.

The large-scale synthetic method of NEt-3IB with a low environmental burden established in this study is expected to help develop new drugs for the treatment of inflammatory bowel diseases. When large-scale synthesis of APIs is generally considered, it is often considered from the search for suitable synthetic routes for large-scale synthesis. On the other hand, based on existing synthetic methods, this approach to convert organic solvents to lipophilic ethers can be expected to promote the development of not only NEt-3IB but also large-scale synthetic methods for low-molecular-weight drug substances, as well as to reduce the environmental impact of the drug substance synthesis process.

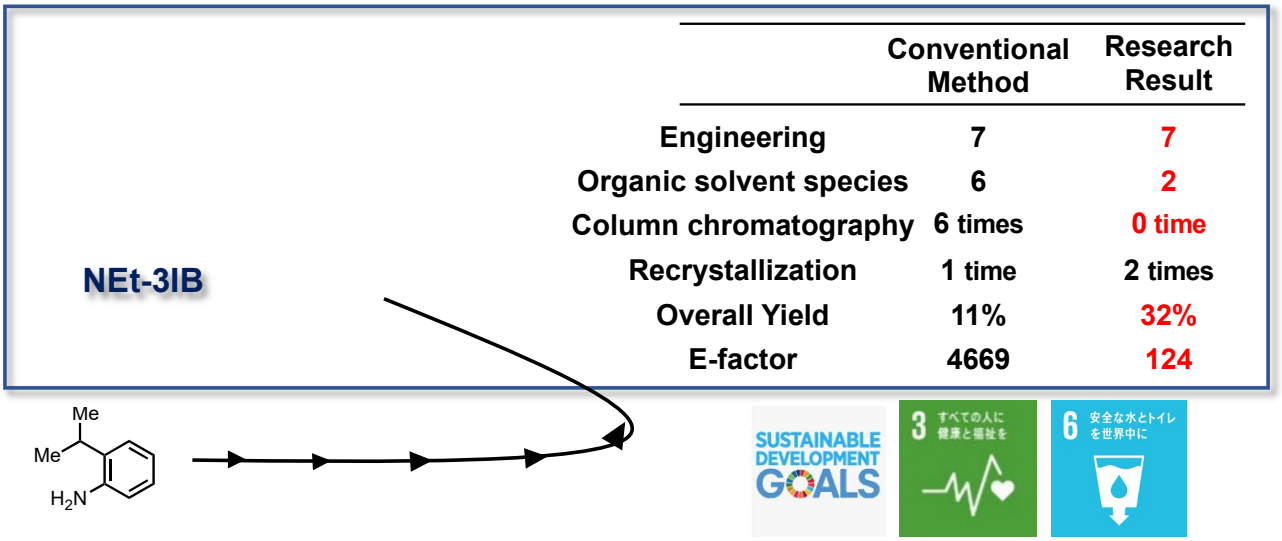

Figure 1. Conceptual diagram of the environmental mass-synthesis method of NEt-3IB created in this study (adapted from the figure in the article).

＜**Social Significance**＞

Inflammatory bowel disease is one of the diseases that has been increasing worldwide, especially among young people in recent years. Antibody drugs are also marketed for the treatment of inflammatory bowel disease, but challenges such as high medical costs and the need for injections and infusions for treatment remain. Considering the global increase of this disease, the development of small molecule pharmaceuticals with a molecular weight less than 500 that can be administered orally is expected to treat inflammatory bowel disease that does not depend on the difference in wealth or the size of the healthcare facility. This will also contribute to "3 Healthy and Wellbeing for All" of the Sustainable Development Goals (SDGs) promoted by this study. From this perspective, NEt-3IB is being developed as a new anti-inflammatory bowel disease agent that can contribute to SDGs, and the results of this study can accelerate drug development.

In organic chemistry, waste such as waste liquid becomes a problem before obtaining the target compounds. In this study, we have developed a synthetic method that allows not only the mass synthesis of NEt-3IB but also the reduction of waste liquid volume. These synthetic methods are expected to contribute to SDGs's "6 Safe Water and Toilets worldwide". Organic synthetic research also emphasizes Green Sustainable Chemistry, and the results of this research, which has drastically reduced the amount of waste liquid, are considered to be of great social significance.

In general, drug development involves the synthesis of small amounts of seed compounds, which are a class of drugs, and the evaluation of their medicinal properties and toxicity is extensive. A desired compound is selected from them and stepped up to non-clinical and clinical studies. From 1, a route search suitable for large-scale synthesis is conducted to assure the amount of compounds required for such studies. In this study, we took an approach to convert the organic solvent used into a fat-soluble ether, leaving the existing synthetic route intact. The reason behind this was the belief that this approach is not limited to NEt-3IB but can be applied to a variety of bulk APIs.

Recently, the recall of pharmaceuticals, such as generic drugs, has become a problem, which is attributed to the contamination of foreign substances in reaction kilns (batches). This has led to worldwide attention to the conversion from batch synthesis to flow synthesis, which can be reacted in a flow-path system. The large-scale synthesis method for NEt-3IB found in this study is simple to purify and reduces the number of organic solvent species used. Therefore, this method is expected to provide a stepping stone for the complete continuous-flow synthesis of APIs, which is preceded by the world.

■Info

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■COI

This study is conducted at the joint research funding of AIBIOS K.K., but is not involved in its study design, data collection, analysis, interpretation, writing of this paper, and decision to post for publication.

◆Comment from Researcher

It is hoped that the results of this study will contribute to SDGs promoted by Okayama University in addition to helping to develop medicines.
As a student of graduate school, able to participate this medical research is an important milestone of my future career. I would like to express my gratitude to Associate Professor Kakuta and all those involved for giving me this opportunity.

Mr. Yuta Takamura

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