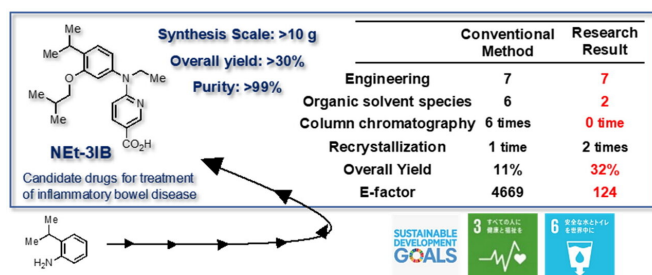


Green synthesis of drug candidate for inflammatory bowel disease

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The new synthesis technique offers higher yields than conventional methods of synthesis and also succeeded in reducing the use of organic solvents, thus making the overall process more sustainable. Credit: Hiroki Kakuta

Inflammatory bowel disease (IBD), characterized by a chronic inflammation of the digestive tract, is currently treated with steroids and antibody drugs. However, steroids have side effects, such as delayed healing, and antibody drugs are expensive. Small-molecule drugs are both cost-effective and easy to administer. A new small-molecule oral drug is key to achieving the sustainable development goal (SDG) "health and well-being for all."

To this end, a research team led by Associate Professor Hiroki Kakuta from Okayama University, Japan, have developed a new large-scale [synthesis](#) method for widespread and stable supply of

4-(ethyl(3-isobutoxy-4-isopropylphenyl)amino)benzoic acid or NEt-3IB, a promising drug candidate for IBD. The research team further consisted of Yuta Takemura, Ken-ichi Morishita, Shota Kikuzawa, and Masaki Watanabe, all from Okayama University. Their findings have been published in *Chemical and Pharmaceutical Bulletin*. The paper was made available online on February 1, 2022 and was published in Volume 70 Issue 2 of the

journal.

"We have successfully developed a new method for mass-synthesizing environmentally friendly NEt-3IB with a 35-fold better E-factor—an indicator of the environmental burden in multistage drug substance synthesis—than conventional processes," says Dr. Kakuta.

Describing the motivation behind their study, Dr. Kakuta explains, "The synthesis of NEt-3IB conventionally uses column chromatography, which requires a large amount of organic solvents in addition to three organic solvents that are not recoverable for reaction. In order to achieve carbon neutrality and meet [sustainable development goals](#) (SDGs), we were driven to avoid column chromatography and find approaches with recoverable [organic solvents](#)."

With this in mind, the research team studied the existing chemical synthesis methods and developed a new process that uses only a fat-soluble ether and alcohol. This modification drastically reduced the volume of liquid waste and also allowed it to be easily recycled. Purification of the resultant NEt-3IB by recrystallization confirmed that this new synthesis method was capable of supplying large quantities of NEt-3IB with a total yield of more than 30% and a purity of 99%.

"Our method provides an example of an approach that employs recoverable solvents and takes a step towards carbon neutrality. This approach can be applied for the production of not only NEt-3IB, but also other small molecule pharmaceuticals," adds Dr. Kakuta.

On a related note, the contamination of reaction kilns, or "batches," by foreign substances has led to plenty of drug recalls worldwide during recent times. This has sparked global curiosity and a [paradigm shift](#) from batch synthesis to flow synthesis. The large-scale flow synthesis method

for NEt-3IB reported in this study involves a simple purification step and reduces the number of organic solvent species used during the entire process.

Owing to these distinct benefits, the newly devised method is expected to provide a stepping stone for the complete continuous-flow synthesis of active pharmaceutical ingredients, popularly known as APIs. Dr. Kakuta explains, "We are going to launch [clinical trials](#) this year using NEt-3IB synthesized via the environmentally-friendly method. We hope to find a new treatment for IBD within a few years."

More information: Yuta Takamura et al, Development of Scaled-Up Synthetic Method for Retinoid X Receptor Agonist NEt-3IB Contributing to Sustainable Development Goals, *Chemical and Pharmaceutical Bulletin* (2022). [DOI: 10.1248/cpb.c21-00911](#)

Provided by Okayama University

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