PRECISION IN MEDICINAL CHEMISTRY: HARNESSING ENZYMES FOR ADVANCED HALOGENATION

Fong Tian Wong, Institute of Molecular and Cell Biology, Singapore
wongft@imcb.a-star.edu.sg
Guang Rong Peh, Institute of Sustainability for Chemicals, Energy and Environment (ISCE^2), Agency for Science, Technology and Research (A*STAR), Republic of Singapore.
Gregory A. Gunawan, Institute of Sustainability for Chemicals, Energy and Environment (ISCE^2), Agency for Science, Technology and Research (A*STAR); Institute of Molecular and Cell Biology (IMCB), Agency for Science, Technology and Research (A*STAR), Republic of Singapore.
Jiawu Bi,Institute of Molecular and Cell Biology (IMCB), Agency for Science, Technology and Research (A*STAR), Republic of Singapore.
Terence Tay, Singapore Institute of Food and Biotechnology Innovation (SIFBI), Agency for Science, Technology and Research (A*STAR), Republic of Singapore.
Elaine Tiong, Institute of Molecular and Cell Biology (IMCB), Agency for Science, Technology and Research (A*STAR), Republic of Singapore.
Lee Ling Tan, Institute of Molecular and Cell Biology (IMCB), Agency for Science, Technology and Research (A*STAR), Republic of Singapore.
Shimin Jiang, Disease Intervention Technology Laboratory, Institute of Molecular and Cellular Biology, Agency for Science, Technology and Research (A*STAR), Singapore.
Yi Ling Goh, Institute of Sustainability for Chemicals, Energy and Environment (ISCE^2), Agency for Science, Technology and Research (A*STAR), Republic of Singapore.
Suming Ye, Institute of Sustainability for Chemicals, Energy and Environment (ISCE^2), Agency for Science, Technology and Research (A*STAR), Republic of Singapore.
Joel Wong, Institute of Sustainability for Chemicals, Energy and Environment (ISCE^2), Agency for Science, Technology and Research (A*STAR), Republic of Singapore.
Chris Brown, Disease Intervention Technology Laboratory, Institute of Molecular and Cellular Biology, Agency for Science, Technology and Research (A*STAR), Singapore.
Huimin Zhao, Singapore Institute of Food and Biotechnology Innovation (SIFBI), Agency for Science, Technology and Research (A*STAR), Republic of Singapore; University of Illinois at Urbana-Champaign, USA.
Ee Lui Ang, Singapore Institute of Food and Biotechnology Innovation (SIFBI), Agency for Science, Technology and Research (A*STAR); National University of Singapore, Republic of Singapore
Yee Hwee Lim, Institute of Sustainability for Chemicals, Energy and Environment (ISCE^2), Agency for Science, Technology and Research (A*STAR); National University of Singapore, Republic of Singapore

Key Words: halogenation; heteroaromatic; X-ray crystallography; flavin-dependent halogenases

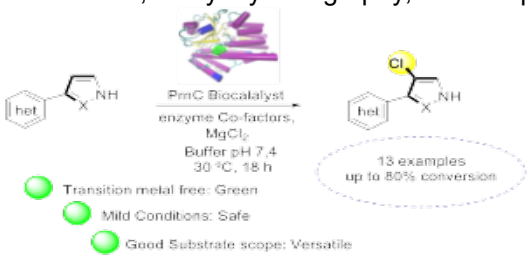

Figure 1. Biocatalysis under benign conditions (adapted from Peh, Guangrong, et al. "Site-selective Chlorination of Pyrrolic Heterocycles by Flavin Dependent Enzyme PrnC." (2022).)

Halogenated natural compounds can possess potent and highly specific biological activities. As a result, the incorporation of halogens has become a common practice in the field of medicinal chemistry, enabling precise adjustments to bioactivity and efficacy. Traditional chemical halogenation methods often entail the use of harsh reagents and frequently yield unwanted multiple halogenated compounds.
In contrast, nature employs a more selective approach to introduce halogens, utilizing metal halide salts and halogenating enzymes under relatively mild conditions.
In light of these considerations, we present recent research findings centered on two classes of halogenases: phenolic halogenase RadH and pyrrolic halogenase PrnC. These enzymes have been effectively harnessed to access a diverse range of halogenated molecules, offering a promising avenue for broadening the scope and enhancing the precision of halogenation techniques in medicinal chemistry and beyond.