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Koki Yamamoto

Structure–Activity Relationships for Development of Neurokinin-3 Receptor Antagonists

Reducing Environmental Impact

Doctoral Thesis accepted by Kyoto University, Kyoto, Japan

Springer

Author
Dr. Koki Yamamoto
Graduate School of Pharmaceutical Sciences
Kyoto University
Kyoto, Japan

Supervisor
Prof. Shinya Oishi
Kyoto University
Kyoto, Japan

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Supervisor's Foreword

It is my great pleasure to introduce Dr. Koki Yamamoto's thesis for Springer Theses. He joined our group at Kyoto University in April 2013 and started his scientific career under the supervision of Prof. Nobutaka Fujii, Prof. Hiroaki Ohno, and myself. During his six-year career at Kyoto University, he performed several structure–activity relationship studies of receptor ligands for neurokinin-3 receptor (NK3R), which regulates reproductive neuroendocrine systems.

His initial project as an undergraduate student focused on the development of novel NK3R antagonist peptides with resistance against proteolytic degradation. He learned a series of technical skills for medicinal chemistry, including solid-phase peptide synthesis and bioassays. In his doctoral studies at the Graduate School of Pharmaceutical Sciences, Kyoto University from 2014, he engaged in the development of selective NK3R antagonists with reduced environmental impact, which could be converted into substance(s) with much lower activity after excretion from the target animal(s). His unique concern was derived from research experience at the Animal Resource Science Center, Graduate School of Agricultural and Life Science, The University of Tokyo, in collaboration with Prof. Kei-ichiro Maeda (The University of Tokyo) and his colleagues in the snow season of 2014. He realized that large portions of bioactive agents were excreted from the target animal(s) and could be released into the natural environment without being metabolized or degraded. To minimize the effect of the bioactive ingredient(s) on non-target animals, he designed novel NK3R antagonists with decreased bioactivity under environmental conditions. During the course of his studies, he also investigated the synthesis of unprecedented heterocycles, which could be employed as scaffolds for novel NK3R antagonists. It should be noted that his scientific contributions included many collaborative works with Prof. Maeda, Prof. Hiroko Tsukamura (Nagoya University), Prof. Satoshi Ohkura (Nagoya University), and their colleagues, in which the in vivo bioactivities of several agents for reproductive functions were investigated.

This comprehensive thesis includes a design concept, chemistry, biological evaluations, and chemical properties, which will be informative for the development of novel NK3R antagonists and for the design of pharmaceutical agents with

reduced environmental impact. He has published three articles related to this thesis in medicinal chemistry journals. I very much appreciate his continuous efforts to achieve the project goals.

Kyoto, Japan
November 2019

Prof. Shinya Oishi

List of Published Articles

Parts of this thesis have been published in the following journal article:

Chapter 2
Koki Yamamoto, Shiho Okazaki, Hiroaki Ohno, Fuko Matsuda, Satoshi Ohkura, Kei-ichiro Maeda, Nobutaka Fujii, Shinya Oishi (2016) Bioorg. Med. Chem. 24:3494–3500.

Chapter 3
Koki Yamamoto, Yasushi Yoshikawa, Masahito Ohue, Shinsuke Inuki, Hiroaki Ohno, Shinya Oishi (2019) Org. Lett. 21:373–377.

Chapter 4
Koki Yamamoto, Shinsuke Inuki, Hiroaki Ohno, Shinya Oishi (2019) Bioorg. Med. Chem. 27:2019–2026.

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