Molecular Conversion Laboratory

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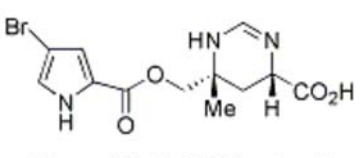
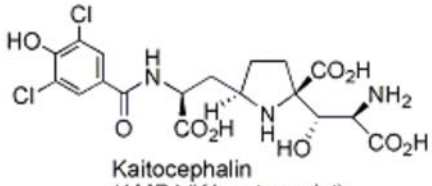
http://www.sci.osaka-cu.ac.jp/chem/henkan/index_e.html

1. Current Research and Principal Research Interests

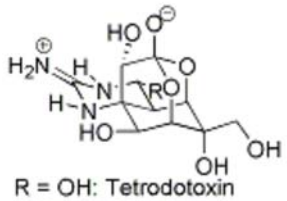
(1) Synthetic Methods and Total Synthesis of Bioactive Natural Products (1980~present)
More than seven hundred amino acids, so-called unusual, unnatural or non-proteinous amino acids, have been found from the nature as a free form or a constituent of peptide. These amino acids have attracted much scientific attention due to their important biological activities such as antibiotics, metal chelators, neurotoxins, and enzyme inhibitors. We have worked continuously on the syntheses of these natural products based on the development of new methods required to overcome the key step for their total synthesis. Representative examples are the total synthesis of mugineic acid (metal chelator from wheat root), domoic acid (neuroexcitatory amino acid from red algae), echinocandin D (anti-fungi and anti-yeast activity from Aspergillus ruglosus), and galantin I (anti-bacterial activity from Bacillus pulvifaciens). Among these studies, methods for the reductive amination to connect amino acid linkage, stereoselective construction of 1,2- and 1,3-amino hydroxy systems, interconversion of amino protective groups via a silyl carbamate, and related methods have been reported (1980-1993). Our recent synthetic efforts have focused on the synthesis of natural products and related artificial amino acids (β -substituted analogs of β -amino acid) possessing an amino group attached to a quaternary carbon center. These compounds have been viewed as having increasing importance not only because of their significant biological activities but also their restricted conformations. We have developed an efficient method for the synthesis of optically active β -substituted amino acids using an asymmetric version of Strecker synthesis. Thus, various types of β -substituted β -amino acids have been synthesized in optically active form, e.g., a potent Leu-enkephalin analog incorporating one of the synthetic β -substituted amino acids, (1R,2S)-1-amino-2-hydroxycyclohexanecarboxylic acid [(1R,2S)-Ahh], the Corey intermediate of lactacystein (neurotropic factor from Streptomyces sp) (1994-1999), a bromopyrrole alkaloid manzacidin A and C (enzyme inhibitor from marine sponge, 2000), kaitocephalin and its 7- and/or 9-epimers (glutamate antagonist, 2004), and 5,6,11-trideoxytetrodotoxin (2005). We are currently working on the total synthesis of tetrodotoxin (ion channel blocker) and amathaspiramide F (antibiotic).



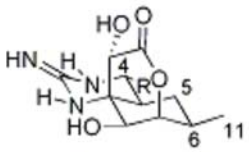
Manzacidin A, B (C5 epimer)
(enzyme inhibitor)



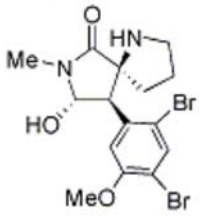
Kaitocephalin
(AMPA/KA antagonist)



R = OH: Tetrodotoxin
(ion channel blocker)



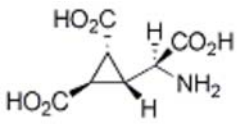
R = OH: 5,6,11-
Trideoxytetrodotoxin



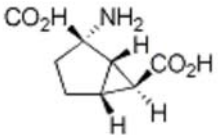
Amathaspiramide F
(antibiotic)

(2) Development of Conformationally Restricted Glutamate Analogs to Investigate Molecular Functions of Neuroexcitaory Amino Acid (EAA) Receptors (1987~present)

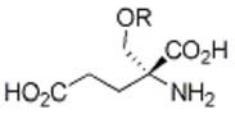
Glutamate receptors at many synapses in mammalian central nervous systems (CNS) are implicated in the construction of memory and early learning as well as in the pathogenesis of neuron damage to cause various neuronal diseases. We have studied the conformational role of glutamate when it binds to the receptors through the synthesis of conformationally restricted analogs of glutamate, i.e., L-2-(carboxycyclopropyl)glycines (CCGs) and their 3'-substituted analogs (MCGs and DCG-IV). This work has demonstrated that not only did the receptors and transporters require a specific conformation of glutamate, but also the analogs can be used as tools for the neuropharmacological research as well as lead compound for neuroptotecting medicine (1987-2000). We, recently, have performed (1) the syntheses of new EAA ligands whose conformations are strictly or partially restricted by a carbocycle or an β-substitition of glutamate using the method described in (a), (2) pharmacological characterization of the synthetic glutamate analogs to glutamate receptors; and (3) exploration of neuroactive amino acids and amines from wasp venom. Thus, several new and sub-type selective agonists for the glutamate receptors have been synthesized (LY354740 and β-hydroxymethyl- and alkoxymethyl-L-glutamate) and a β-carbon analogs of threo-β-hydroxy aspartate and β-benzyl aspartate by the use of a [3.3] sigmatropic rearrangement of β-acyloxysilane.



DCG-IV
(mGluR2 agonist)



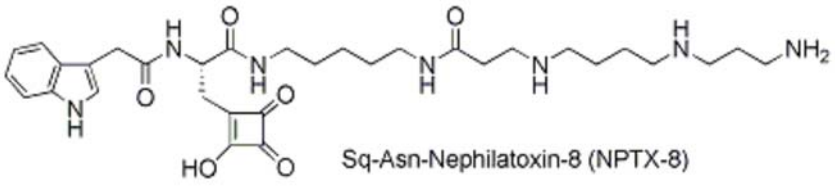
(+)-LY354740
(mGluR2 agonist)



R = H, Me, or Bn
(mGluR2 antagonist)

(3) Chemical Studies on 3,4-Diohydroxy-3-cyclobutenedione (Squaric Acid) as a Multiple Functional Group. Development of Squaryl Group-Containing Bioactive Molecules (1995-present)

The 4-hydroxy-2,3-dioxocyclobut-1-enyl group (squaryl (Sq) group) is characterized by its strong acidity (pKa = 1), aromaticity, and chelating ability with metals. We envisioned that SQ group can be utilized as an isostere of carboxylic acid and as a marker molecule for analyzing peptide sequences. Initial approach was its incorporation into the γ-position of glutamate connected with a carbon-carbon bond to obtain molecular stability against hydrolysis (1995-2000). Recent progress is summarized as follows: (1) incorporation of SQ-containing glutamate and aspartate into spider and wasp polyamines. SQ-Asp-containing NPTX-8 exhibited paralytic activity to cricket which was much potent than natural NPTX-8, (2) synthesis of β-amino squaric acid as an isostere of various β-amino acid using an addition of dianion enolate derived from β-amino acid ester to diisopropylsquarate as the key step, and (3) chemoselective introduction of the squaryl group into the N-terminal of biologically active peptide for simplifying the amino acid sequencing by MS/MS analysis) (2001-2005).



2. Selected Publications

1. "Total Synthesis of (-)-Kaitocephalin", M. Kawasaki, T. Shinada, M. Hamada, and Y. Ohfune, *Org. Lett.*, **7**, 4165-4167 (2005).

2."Asymmetric Strecker Route toward the Synthesis of Biologically Active -α, α-Disubstituted β-Amino Acids", Y. Ohfune and T. Shinada., *Bull. Chem. Soc. Jpn.*, **76**, 1115-1129 (2003).

3."Total Synthesis and Absolute Structure of Manzacidin A and C", K. Namba, T. Shinada, H. Teramoto and Y. Ohfune, *J. Am. Chem. Soc.* , **122**, 10708-10709 (2000).

4. "Efficient Synthesis of a Novel 4-Hydroxy-2,3-dioxocyclobut-1-enyl Group Containing Amino Acids", T. Shinada, K. Hayashi, T. Hayashi, Y. Yoshida, M. Horikawa, K. Shimamoto, Y. Shigeri, N. Yumoto, and Y. Ohfune, *Organic Lett.*, **1**, 1663-1666 (1999).

5. "Synthesis and Conformational Analysis of Glutamate Analogs. 2-(2-Carboxy-3- substituted-cyclopropyl)glycines as Useful Probes for Excitatory Amino Acid Receptors", K. Shimamoto and Y. Ohfune, *J.Med. Chem.* , **39** , 407-423 (1996).

6. "Efficient Syntheses of the Four Enantiomers and Diastereomers of α-Methylthreonine and Both Enantiomers of α-Methylserine", S.-H Moon and Y. Ohfune, *J. Am. Chem. Soc.*, **116**, 7405-7406 (1994).

7. "Synthesis of L-2-(2,3-Dicarboxycyclopropyl)glycines. Novel Conformationally Restricted Glutamate Analogues", Y. Ohfune, K. Shimamoto, M.Ishida, and H. Shinozaki, *Bioorg. Med. Chem. Lett.*, **3**, 15-18 (1993).

8. (a) "Syntheses and Reactions of Silyl Carbamates. 1. Chemoselective Transformations of Amino Protecting Groups", M. Sakaitani and Y. Ohfune , *J. Org. Chem.*, **55**, 870- 876 (1990). (b) "Syntheses and Reactions of Silyl Carbamates. 2. A New Mode of Cyclic Carbamate Formation from tert-butyldimethylsilyl Carbamate", M. Sakaitani and Y. Ohfune , *J. Am. Chem. Soc.*, **112**, 1150-1158 (1990).

9. (a) "Total Synthesis of Echinocandins. 1. Stereocontrolled Syntheses of the Constituent Amino Acids", N. Kurokawa and Y. Ohfune, *J. Am. Chem. Soc.*, **108**, 6041-6043 (1986). (b) "Total Synthesis of Echinocandins. 2. Total Synthesis of Echinocandin D via Efficient Peptide Coupling Reactions", N. Kurokawa and Y. Ohfune, *J. Am. Chem. Soc.* , **108**, 6043-6045 (1986).

10. "Total Synthesis of (-)-Domoic Acid. A Revision of the Original Structure", Y. Ohfune and M. Tomita, *J. Am. Chem. .Soc.*, **104**, 3511-3513 (1992).

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