Department of Chemogenomics and Bioorganic Medicinal Chemistry

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Research Projects:

The phenomena of life are driven by well-regulated chemical reactions and equilibrium of many organic compounds. Abnormalities in this regulation can cause disease, and organic compounds are often used as the medicine to treat disease. It is thus essential to understand the underlying organic chemistry of drug discovery and treatment of disease. Since highly effective medicines have already been developed for many druggable therapeutic targets, we have to consider how to discover drugs for difficult-to-treat diseases. This challenging situation can be solved by making available compounds that are hard to synthesize with existing methods in drug discovery, or by controlling the interaction of biomolecules that have hitherto been difficult to control. In our laboratory, the following research projects are underway that focus on organic chemistry-driven drug discovery.

1) Synthesis of structurally complex bioactive compounds: Small molecule drug discovery has become increasingly challenging. Despite advances in combinatorial synthesis and high-throughput screening, such technologies still have limitations. Another problem is the lack of therapeutic targets since drugs have already been developed for many diseases. Our approach is to use complex molecules to target biomolecular interactions that have not yet been probed in drug discovery. We are interested in the synthesis of biologically-active compounds, such as alkaloids containing highly complex ring systems, and macrocyclic peptides.

2) Novel methods for the synthesis of complex structures and their applications: Structure-activity relationship (SAR) studies and structural optimization are needed to improve the biological activity and bioavailability of potential drug candidates. This becomes very costly in terms of time and money when using very complex molecules. We are developing new synthetic methodologies that can be used to construct complex core structures commonly found in biologically active molecules. We are particularly interested in atom-economic transition metal catalysis using elements such as gold and palladium. Such methodologies are applied to drug discovery and structural studies to evaluate the utility of the developed reactions.

3) Identification of functional molecules based on designs, synthetic studies and chemical modifications of biomolecules: Biomolecules such as glycans, lipids, and peptides possess a wide range of biological activities, and are involved in various physiological functions and pathological conditions. By implementing rational designs, synthetic studies and chemical modifications on the basis of organic chemistry and bioorganic chemistry, we aim to develop functional molecules that can modulate and help us understand physiological functions and pathologies. Furthermore, by using these functional molecules as biological probes, we investigate the localization and intracellular behavior of target molecules for the elucidation of biological mechanisms and the discovery of new drug leads.

4) Development of a novel screening platform using synthetic peptides and proteins: Recombinant DNA technology facilitates the preparation of peptides and proteins. In contrast, chemical synthesis of peptides and proteins *via* the stepwise assembly of amino acids and/or chemical ligation can provide an alternative approach for the preparation of bioactive peptides with unique structures (secondary metabolites) and peptides/proteins containing post-translational modifications. Using these synthetic peptides and proteins, we are developing a unique screening platform to identify unprecedented drug leads from unexplored classes of substances.

5) Drug screening programs using in-house chemical libraries: Identification of novel bioactive compounds as drug candidates is an important subject in drug discovery. We have synthesized natural products with unique bioactivity (e.g. alkaloids) and biomolecules with important physiological functions (e.g. peptide hormones) and constructed a chemical library containing these compounds. Synthetic intermediates of these functional molecules are also included in our library. These compounds cannot be obtained commercially and we are engaged in a number of ongoing collaborative screening projects.

Recent publications

- Inuki *et al.* Construction of Quaternary Carbon Stereocenter of α-Tertiary Amine through Remote C–H Functionalization of Tris Derivatives: Enantioselective Total Synthesis of Myriocin. *Org. Lett.*, **21**, 5485 (2019).
- Ohno *et al.* Gold(I)-Catalyzed Cascade Cyclization Reactions of Allenynes for the Synthesis of Fused Cyclopropanes and Acenaphthenes. *Angew. Chem. Int. Ed.*, **58**, 7792 (2019).
- Oishi *et al.* Development of Mirror-Image Screening Systems for XIAP BIR3 Domain Inhibitors. *Bioconjug. Chem.*, **30**, 1395 (2019).
- Inuki *et al.* Potent Th2 Cytokine-Bias of Natural Killer T Cell by CD1d Glycolipid Ligands Based on "Anchoring Effect" of Polar Groups in Their Lipid Component. *Angew. Chem. Int. Ed.*, **57**, 9655 (2018).
- Ohno *et al.* Direct Synthesis of Aryl-Annulated (c)Carbazoles by Gold(I)-Catalysed Cascade Reaction of Azide-Diynes and Arenes. *Chem. Sci.*, **9**, 8416 (2018).
- Oishi *et al.* Structure–Activity Relationship Study of Cyclic Pentapeptide Ligands for Atypical Chemokine Receptor 3 (ACKR3). *J. Med. Chem.*, **61**, 3745 (2018).