AL03 Medicinal Chemical Study Based on Theoretical Design of Biologically Active Compounds

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Different from studies of pharmaceutical industries that should be productive, achademic medicinal chemistry studies should be theoretical, namely, science. From this viewpoint, we have worked on studies based on theoretical design of biologically active compounds. In addition, we have developed new reactions and synthetic methods, because "to synthesize compounds that we want to obtain", excellent organic chemistry studies are essential for the medicinal chemistry. In this lecture, I would like to introduce our studies summarized below.

1. Three-dimensional diversity-oriented studies based on the structural feature of cyclopropane[1)]

Efficient conformational restriction of structurally flexible bioactive compounds can improve the affinity and selectivity for the target biomolecule. Thus, we presented a strategy that is "design and synthesis of a series of the cyclopropane conformationally restricted analogues with three-dimensional structural diversity provides the analogue having the bioactive conformation, even if the structure of the target biomolecule is unknown". In the strategy, the three structural features of cyclopropane, *i.e.*, *cis/trans* restriction, cyclopropylic strain, and bisected conformational preference are combinationally used. By the strategy, we have developed biologically active compounds for a wide variety of the target biomolecules, such as, NMDA receptor antagonists, histamine H_3 receptor agonists and antagonists, BASE1 inhibitors, proteasome inhibitors, resolvin E2 stable equivalents, and membrane permeable cyclic peptides. These results demonstrated that the strategy is generally effective for the identification of bioactive compounds for desired target biomolecules.

2. Medicinal chemistry on Ca^{2+}-mobilizing second messengers[2)]

We hypothesized that biomolecules in intramolecular signal transduction systems are potential drug targets. Thus, we focused on Ca^{2+}-mobilizing second messengers cyclic ADP-ribose (cADPR) and *myo*-inositol trisphosphate (IP_3). Because cADPR is chemically and biologically very unstable and its function has not been clarified enough, we developed carbocyclic ribose and thioribose analogues of cADPR, *i.e.*, cADPcR and cADPtR lacking the unstable N1-ribosiyl linkage. cADPcR and cADPtR are biologically and chemically stable and active like cADPR in various cell systems. We also developed D-glucose based IP_3 mimics with IP_3-like Ca^{2+}-mobilizing potency. These compounds developed are useful as biotools to investigate the intramolecular signal transduction systems.

3. Organic chemistry for the medicinal chemistry studies[3)]

Organic chemistry is a counterpart for theoretical drug design to practice excellent medicinal chemistry studies. We provided methods for preparing various chiral cyclopropanes that were construction of cyclopropane rings, coupling and C–H activation reactions on cyclopropane rings, construction of asymmetric carbon centers adjacent to cyclopropane rings, and cyclopropane amino acid synthesis. Also radical reactions with silicon tethers for stereo- and regioselective introduction of carbon-chains, which have been effectively used in sugar and nucleoside chemistries. Stereoselective glycosidations based on the controlling anomeric effect due to conformational restriction of substrates were also developed. During these studies, we presented the cyclopropane bisected conformation-based transition state model for nucleophilic additions and the penta-valent silicon radical transition state model in radical rearrangement reactions, which are effective to understand the reaction mechanisms.

1) For examples, *J. Med. Chem.* **1998**, *41*, 3507. *J. Med. Chem*. **2003**, *46*, 1980. *Org. Lett*. **2008**, *10*, 3571. *J. Med. Chem*. **2010**, *53*, 3585. *J. Med. Chem.* **2012**, *55*, 8838. *Org. Lett.* **2013**, *15,* 1686. *J. Med. Chem.* **2013**, *56*, 3689. *Chem. Commun*. **2014**, *50*, 244. *Org. Lett.* **2016**, *18*, 6224. *Chem. Eur. J*. **2017**, *23*, 3034. *Chem. Eur. J*. **2017**, *23*, 14394.
2) For examples, *J. Org. Chem*. **2000**, *65*, 5238. *J. Am. Chem. Soc*. **2001**, *123*, 8750. *J. Med. Chem*. **2003**, *46*, 4741. *J. Am. Chem. Soc*. **2005**, 127, 8846. *J. Med. Chem*. **2006**, *49*, 1900. *J. Med. Chem*. **2006**, *49*, 5750. *Angew. Chem. Int. Ed.,* **2013***, 52,* 6633. *J. Org. Chem.* **2015**, *80*, 6619 *J. Med. Chem*. **2016**, *59*, 7282. *J. Med. Chem.* **2017**, *60*, 5868.
3) For examples, *J. Org. Chem*. **1996**, *61*, 915. *J. Org. Chem*. **1997**, *62*, 5676. *J. Am. Chem. Soc*. **2000**, *122*, 1343. *J. Am. Chem. Soc*. **2001**, *123*, 11870. *J. Org. Chem*. **2002**, *67*, 166. *Angew. Chem. Int. Ed*. **2002**, *41*, 4748. *Angew. Chem. Int. Ed*. **2003**, *42*, 1021. *Org. Lett.* **2004**, 6, 3751. *Org. Lett.* **2013**, *15*, 6202. *Org. Lett*. **2016**, *18*, 48. *J. Org. Chem*. **2017**, *82*, 25.