26G-ISMS43 **Discovery of Novel 5,6,7,8-tetrahydro[1,2,4]Triazolo[4,3-*a*]Pyridine Derivatives as *γ*-secretase Modulators**

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γ-Secretase modulators (GSMs), which lower pathogenic amyloid beta (A*β*) without affecting the production of total A*β* or Notch signal, have emerged as a potential therapeutic agent for Alzheimer's disease (AD). A novel series of 5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine derivatives was discovered and characterized as GSMs. The optimization study using ligand-lipophilicity efficiency (LLE) as a drug-likeness guideline led to identification of various types of high-LLE GSMs with potent in vivo Aβ_{42}-lowering effects by single administration. Furthermore, multiple oral administration of the representative compound significantly reduced soluble and insoluble brain Aβ_{42}, and ameliorated cognitive deficit in novel object recognition test (NORT) using Tg2576 mice as an AD model.