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A novel compound of pyrrolidone derivatives as a M1 muscarinic acetylcholine receptor agonist and its application to Alzheimer's disease

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Muscarinic acetylcholine receptors (mAChRs) are widely expressed in the central nervous system (CNS) and modulate multiple neuronal functions. The predominant type of mAChRs in the CNS is the M_1 subtype, and M_1 mAChR is located in the cerebral cortex and hippocampus. Both of these brain areas are known to be important for cognition, learning and memory and to develop amyloid plaques in Alzheimer's disease. Based on these observations, it has been suggested that the M_1 mAChR has long been viewed as a potential therapeutic target for the treatment of Alzheimer's disease and other CNS disorders.

Herein, we described the synthesis of pyrrolidone derivatives and assayed them against all five subtypes (M_1 - M_5) of mAchRs. Using an FDSS6000 96-well fluorescence plate reader, we assayed 18 pyrrolidone derivative compounds in HEK293 cells transiently transfected with each human mAchR. In the presence study, we found compound KK1259 is a potent and selective agonist of M_1 mAchR. Furthermore, we examined the effect of compound KK1259 on extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation and a computational mapping of compound KK1259 into 6-feature 3D pharmacophore hypothesis to acquire more information about structure-activity relationships.

Biography

Hyewhon Rhim has completed her Ph.D. at the age of 33 years from the University of Chicago and postdoctoral studies from the University of Chicago and Seoul National University. She is a Principal Research Scientist, Center for Neuroscience, Brain Science Institute Korea Institute of Science and Technology in Seoul, Korea. She has published more than 130 papers in reputed journals and 50 domestic and international patents.

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