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Design, synthesis and biological activity of α -Ketoglutarate analogues as KDM5A inhibitors

○ Jiranan CHOTITUMNAVEE[1], Benjaporn BURANRAT[1], Yukihiro ITOH[1], Takayoshi SUZUKI[1] ([1]Kyoto Prefectural University of Medicine)

Introduction: Histone lysine demethylases (KDMs) play a role in the demethylation of histone lysine residues. Two families have been identified which are flavin-dependent lysine demethylases and Jumonji C-containing (JmjC) lysine demethylases. The JmjC lysine demethylases are Fe (II)/α-ketoglutarate (αKG)-dependent oxygenases. KDM5A, an isoform of the JmjC lysine demethylases removing the di-and tri-methylation mark of lysine 4 on histone 3 (H3K4), overexpresses in several human cancer cells. In addition, it has been reported to be involved in tumor formation, metastasis and advance of drug resistance in human cancers, suggesting KDM5A as a potential target for cancer treatment. Therefore, the KDM5A was chosen as a target KDM in this work. In this study, we designed αKG analogs as JmjC lysine demethylase inhibitors since αKG acts as a crucial cofactor of these enzymes.

Method: The αKG analog was designed and synthesized. The inhibitory activity was evaluated by an AlphaScreen KDM5A enzymatic assay, and western blotting analysis was performed to examine the methylation level change of H3K4 in A549 lung cancer cell lines.

Result and Conclusion: The results of the enzymatic assay and western blotting analysis showed an αKG analog inhibited KDM5A activity significantly and its prodrug enhanced the methylation of H3K4 in a dose-dependent manner in A549 lung cancer cell lines. Thus, the αKG analog is a promising lead for KDM5A inhibitors.