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UP AND DOWN IN HISTONE METHYLATION: IDENTIFICATION OF FIRST-IN-CLASS DUAL G9A/LSD1 INHIBITORS

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In humans, histone methylation pattern results from the balance between lysine methylation and demethylation. LSD1 is a histone demethylases able to remove methyl groups from H3K4me1/2 marks and is part of a repressive complex including also REST and HDAC1/2. This enzyme plays a crucial role in the epigenetic modulation of gene expression resulting overexpressed in several types of tumours. An increase in methylation level induced by the H3K9 histone methyltransferase G9a is equally associated with the onset of various tumours. Therefore, both enzymes represent a valuable target in cancer chemotherapy. Our investigation of quinazolines as H3K9 methyltransferase/demethylase inhibitors led us to identify MC3774, a Lys-mimicking derivative displaying dual G9a/LSD1 inhibition. In particular, MC3774 showed IC50 values of 1.2 and 0.44 μM on G9a and LSD1, respectively. In MV4-11 leukemia cells, MC3774 showed anti-proliferative activity with IC50 = 0.89μM. Considering these observation, we worked on the synthesis of several analogues of MC3774, by inserting at the C2 quinazoline position alkylamino functions with different length and at the C4 position various aryl-alkyl functions, with the aim to increase the selectivity towards LSD1 and to improve the potency in AML cells.

BIOGRAPHY

Antonello Mai has completed his PhD in 1990 from Sapienza University of Rome, Italy. He is Full Professor on Medicinal Chemistry, President of the Master Degree Course of Medicinal Chemistry and Technology in Sapienza University of Rome since 2011 and Member of the Committee for the evaluation of PhD Courses in Sapienza. He has over 280 publications that have been cited over 8500 times and his publication H-index is 50 and has been serving as an Editorial Board Member of reputed journals.

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