Oral Presentation

Pharmacophore-Based Screening and Design of Small Molecule Inhibitors of Protein Arginine Methyltransferases for Cancer Therapy

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ABSTRACT: Chemical modifications of the chromatin, which include DNA methylation and histone modifications, have been established as an important epigenetic mechanism for control of cell proliferation, differentiation, and development. Histone arginine methylation is mediated by protein arginine methyltransferases (PRMTs) that catalyze the transfer of the methyl group from S-adenosyl-L-methionine (AdoMet, SAM) to the guanidino group of arginine residues in protein substrates, resulting in mono and di-methylarginine residues in substrate proteins. Several PRMT enzymes have been validated as new disease biomarkers and therapeutic targets in various cancer models. We developed PRMT-selective inhibitors with diamidine structural scaffolds through virtual screening and followed by rational design. A number of compounds showed low micromolar or submicromolar potency in biochemical PRMT inhibition. Structure-activity relationship (SAR) of the diamidine compounds in PRMT inhibition was obtained. Several top lead molecules are demonstrated to possess excellent anti-tumor activities, especially blocking cell proliferation in leukemia cell lines with different genetic lesions. The disclosed small molecule PRMT inhibitors will be useful chemical probes to investigate new functions of PRMTs and for further therapeutic development.

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