Designing Sinefungin Scaffolds as Specific Protein Methyltransferase Inhibitors

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Abstract: Protein methyltransferases (PMTs) regulate numerous epigenetic processes and are frequently hijacked indiseases, in particular cancer, to initialize or maintain the associated pathogenic phenotypes. With the increased evidence of the roles of PMTs in cancers, tremendous efforts have been made to search for selective PMT inhibitors. However, few selective small-molecule PMT inhibitors have been documented to date, impairing our ability to advance single-agent or combination cancer therapy through intervening these emerging epigenetic targets. Our recent progress in elucidating sinefungin analogues as selective PMT inhibitors allowed us to formulate the current hypothesis that even closely-related PMTs can process distinct conformational states, though not obvious for apo-enzymes, and thus be selectively recognized by small molecule inhibitors that exploit these conformations. This proposal aims to expand substantially on the preliminary finding by screening structurally-diverse sinefungin analogues against conformation landscapes of > 60 human PMTs. Our multi-dimensional approach integrates with *in silico* simulation, small-molecule microarrays (SMMs) and *in vitro* biochemical characterization to establish the streamline of lead identification, scaffold optimization and off-target analysis of PMT inhibitors. Newly discovered PMT inhibitors of high potency and specificity, together with previously identified compounds (preliminary results), will be evaluated in relevant cellular and preclinical experiments. This proposal is expected to formulate an unprecedented strategy to rapidly assess PMT inhibitors and present suitable lead compounds for translational studies with cancer therapy as the long-term goal.