TITLE: Development of Novel Inhibitors Targeting Epigenetic Enzymes

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Introduction: The recently established field of epigenetics assists in filling the holes that cannot be answered by modern genetics. Epigenetics encompasses processes related to gene expression beyond the genetic code itself. It provides a comprehensive understanding that connects the environment, nutrition and heredity. In a direct link to human health, epigenetic changes are associated with complex diseases such as cancer and diabetes. These potentially harmful abnormalities root primarily from DNA methylation or post-translational modifications of histone proteins. Among the various histone modifications, methylation mediated by protein arginine methyltransferases (PRMTs), a class of epigenetic enzymes, plays a critical role in gene regulation. Further insight on the regulation of PRMTs may reveal therapeutic approaches to disease through epigenetic enzyme inhibition. In this study, we investigated cyclic H4 peptides as novel inhibitors of PRMTs and assayed their inhibitory potential.

Methods: Linear modified H4-20 peptides were synthesized utilizing an automated Fmoc solid phase peptide synthesis (SPPS) strategy in which peptides are synthesized from the C - terminal of an amino acid to the N - terminal using an orthogonal protecting group strategy. Subsequently, these modified H4-20 peptides were cyclized by a thioalkylation side - chain reaction. These peptides were purified through reverse-phase high performance liquid chromatography (RP-HPLC) and characterized through matrix-assisted laser desorption ionization (MALDI) mass spectrum analysis. The inhibitory potential of these peptides to enzymes PRMT1 and PRMT5 were evaluated through a scintillation proximity assay.

Results: Several pure, cyclic H4-20 peptides were successfully synthesized through a combination of Fmoc SPPS and a thioalkylation reaction and were verified through MALDI-MS analysis. For one cyclic peptide, the half maximal inhibitory concentration (IC_{50}) for PRMT1 was determined to be 7.9 µM and no IC_{50} for PRMT5 was determined as there was no correlation of the peptide inhibiting PRMT5.

Conclusions: Cyclic peptide analogs of the H4-20 peptide may be a promising class of selective PRMT 1 inhibitors. Further synthesis, characterization and study of these cyclic peptides to improve their biological activities may be instrumental in improving the potential of this class of inhibitors.