Synthesis and evaluation of carbocyanine dyes as PRMT inhibitors and imaging agents

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Introduction

Protein arginine methyltransferase (PRMT) promotes cancer-causing post-translational modifications and has been recognized as a target for developing anti-cancer therapeutics. Arginine methylation is facilitated by PRMTs that use S-adenosyl-L-methionine as the methyl donor to modify the guanidinium side chain of specific arginine residues, which results in mono- and di-methylated arginine residues. Small chemical probes that target PRMTs with strong affinity and selectivity can be used to reveal biological mechanisms of arginine methylation and establish the role of PRMT proteins in a disease pathway. The purpose of this study was to synthesize and evaluate monocationic trimethine cyanine compounds that have potential application in PRMT studies as enzyme inhibitors and as contrast agents for fluorescence microscopy.

Methods

Through the synthetic modification of trimethine cyanine dyes, several hydrophobic derivatives were developed in good yields utilizing ethyl, butyl, and phenylpropyl halides for nitrogen alkylation of the heterocyclic moieties. These cyanine compounds were investigated by screening their anti-methyltransferase activity. The degree of diminishment in PRMT activity was used as a parameter to evaluate the potency of the compounds in inhibiting PRMT1 and PRMT5-mediated arginine methylation. The IC_{50} values of the most promising inhibitors were derived from the dose response curve as the concentration of half-inhibition. Optical and fluorescent microscopies, cell proliferation and flow cytometry assays were used to study the functions of the most potent compounds.

Results

Several of the trimethine cyanine compounds synthesized for this study showed low-micromolar anti-PRMT1 and anti-PRMT5 activity. The promising IC_{50} values are currently helping us generate a structure-activity relationship (SAR) for the general cyanine scaffold for developing more potent anti-cancer agents.

Conclusion

Because PRMT proteins impact a number of disease pathways, the development of novel potent small molecule inhibitors of PRMTs is highly desired. Carbocyanine molecules containing different heterocylic moieties and hydrophobic substituents have been synthesized and several possess micromolar potency for PRMT1 and PRMT5 inhibition that should be further investigated to develop nanomolar inhibitors.

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