Lipophilic lysine-spermine conjugates are potent polyamine transport inhibitors for use in combination with a polyamine biosynthesis inhibitor

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- PMID: 19281226
- PMCID: PMC2714422
- DOI: 10.1021/jm801580w

https://pubmed.ncbi.nlm.nih.gov/19281226/

Abstract

Cancer cells can overcome the ability of polyamine biosynthesis inhibitors to completely deplete their internal polyamines by the importation of polyamines from external sources. This paper discusses the development of a group of lipophilic polyamine analogues that potently inhibit the cellular polyamine uptake system and greatly increase the effectiveness of polyamine depletion when used in combination with DFMO, a well-studied polyamine biosynthesis inhibitor. The attachment of a length-optimized C(16) lipophilic substituent to the epsilon-nitrogen atom of an earlier lead compound, D-Lys-Spm (5), has produced an analogue, D-Lys(C(16)acyl)-Spm (11) with several orders of magnitude more potent cell growth inhibition on a variety of cultured cancer cell types including breast (MDA-MB-231), prostate (PC-3), melanoma (A375), and ovarian (SK-OV-3), among others. These results are discussed in the context of a possible membrane-catalyzed interaction with the extracellular polyamine transport apparatus. The resulting novel two-drug combination therapy targeting cellular polyamine metabolism has shown exceptional efficacy against cutaneous squamous cell carcinomas (SCC) in a transgenic ornithine decarboxylase (ODC) mouse model of

skin cancer. A majority (88%) of large, aggressive SCCs exhibited complete or nearly complete remission to this combination therapy, whereas responses to each agent alone were poor. The availability of a potent polyamine transport inhibitor allows, for the first time, for a real test of the hypothesis that starving cells of polyamines will lead to objective clinical response.