Retrovirology

Poster presentation

Improvement of Polybiguanide-based Microbicides Using Computational Design Methodologies

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Polyethylene hexamethylene biguanide (PEHMB), a polybiguanide compound under development as a topical microbicide effective against HIV-1, was used as a starting point for rational design strategies and novel computational methods focused on identifying similar compounds with greater safety and activity. To investigate the hypothesis that PEHMB may represent a specific 3-D conformation and a degree of chain flexibility that confers the ability to inhibit HIV-1 infection through interactions with HIV-1 co-receptors, patented molecular calculation software (Shape Signatures) was used to predict bioisosteres of PEHMB. These analyses suggested that substitution of a bithiazole group for the ethylene spacers of PEHMB would provide backbone rigidity, nitrogen atom spacing, and electrostatic potentials similar to PEHMB. The resulting molecule, poly(hexamethylene-c-2, 2'-diamino-5, 5'-bithiazole (PHDB), was found to have similar cytotoxicity yet greater activity than PEHMB. These studies strongly support our strategy of design and synthesis of second-generation compounds based on the PEHMB motif.