152

Anti-HBV Nucleotide Prodrug Analogs: Synthesis, Bioreversibility, and Cytotoxicity Studies

Seetharamaiyer Padmanabhan, John Coughlin, Guangrong Zhang, Cassandra Kirk, Radhakrishnan Iyer*

Spring Bank Technologies, Inc., 113, Cedar Street, Suite S-7, Milford, MA 01757, USA

E-mail address: kiyer@springbanktech.com (R. Iyer).

The dinucleoside phosphorothioate, SB 9000, has been identified as a novel anti-HBV agent. Studies in rats and mice have revealed SB 9000 is not orally bioavailable. The lack of oral bioavailability of nucleotides may be due to several factors including: (a) degradation of the compound in the GI tract, and (b) the lack of permeation through the mucosal barrier.

To develop orally bioavailable SB 9000, we carried out the synthesis and evaluation of several prodrugs including S-functionalized analogs of a model dinucleotide. Three classes of S-functionalized analogs were examined: (a) S-(acyloxyalkyl) thiophosphate analogs (b) The S-(acyloxyaryl)thiophosphate analogs, and (c) S-alkyl derivatives with a terminal functional group. Our design of prodrug derivatives was based upon the ability of a target enzyme to unmask a latent functionality to reveal SB 9000 in vivo.The prodrug derivatives were synthesized by chemoselective S-alkylation of the Rp,Sp SB 9000 with the corresponding iodo-, or bromo-intermediates. SB 9000 was synthesized using solid-phase phosphoramidite chemistry, in conjunction with a specially fabricated LOTUS reactorâ. The nucleoside-loaded CPG support was prepared using our recently discovered ultra fast functionalization and loading of solid supports.

Upon incubation with rabbit serum, a few prodrugs were found to undergo enzyme-mediated conversion to SB 9000 with half-lives ranging from 1 to 3 h. Cytotoxicity analysis in a panel of cell lines including, MDBK, Vero, and HFF revealed that in most instances, their CC50 was >1000 micromolar. Following the examination of their stability in simulated gastric fluid and simulated intestinal fluid, selected analogs were evaluated for oral bioavailability in mice.

In conclusion, we have synthesized and evaluated a number of SB 9000 prodrugs as promising candidates for further evaluation as orally bioavailable antiviral agents.

Acknowledgement

Support of this research from NIH (NIAID) under a Research Project Cooperative Agreement Grant Award UO1 AI058270, is gratefully acknowledged.

doi:10.1016/j.antiviral.2007.01.164