NUCLEOTIDES AS ANTI-HBV AGENTS.

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New chemical entities with novel mechanisms are urgently needed for use either alone or in combination with other agents for anti-HBV therapy. As a unique drug discovery strategy against HBV, a library of about 800 nucleotide compounds (prepared using parallel combinatorial approach) was screened for anti-HBV activity using the chronically HBV producing cell line 2.2.15. Through an iterative process of synthesis, and lead optimization, SB-9000 was identified, as a potent anti-HBV nucleotide analog. Although the compound inhibited the replication of both strands of HBV DNA, its 5'-triphosphate analog did not appear to be a chain terminator. Furthermore, SB-9000 did not induce suppression of HBV protein synthesis or intracellular core particle formation. Thus, the compound appears to cause inhibition of the HBV reverse transcriptase-directed priming step prior to elongation of the first viral strand. SB 9000 has high safety index, as evaluated in a panel of cell lines, and is a highly selective anti-HBV agent.

In transient transfection assays, SB-9000 inhibited the replication of 3TC-resistant HBV. In combination treatments, favorable interactions were noted for SB-9000 with 3TC (synergistic) and with ADV (additive). The compound was found to be metabolically stable in serum, and liver microsomes (mouse, rabbit, and human). Pharmacokinetic studies in mice and woodchuck have demonstrated that the compound is stable in plasma and is excreted practically unchanged (by LC-MS/MS) in urine following IV administration.

In transgenic mice expressing HBV, SB-9000 significantly reduced liver HBV DNA at minimal effective dose of 0.5 to 1.6 mg/Kg bodyweight/day. Recently, orally bioavailable prodrug analogs have been synthesized. Preliminary studies in transgenic mice have shown that orally administered SB 9000 prodrug caused significant reduction in liver HBV DNA. SB 9000 represents an exciting, new class of anti-HBV agent. IND-enabling studies of SB 9000 prodrug are in progress.

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