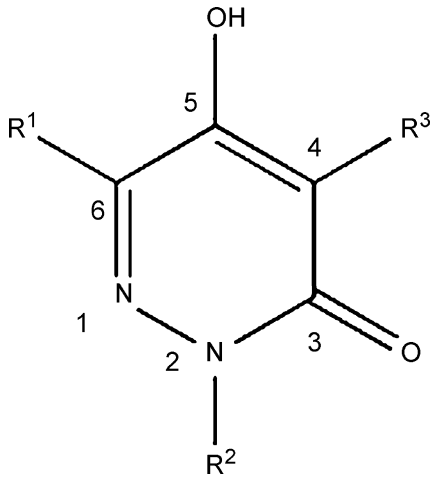

Fig. 1.

Results: Described here are the structure-activity relationships observed by varying the 2- and 6-substituents of our 5-hydroxy-3(2*H*)-pyridazinone NS5B inhibitors. We observed that small heteroaromatic rings and alkyl groups were optimal 6-substituents. We also noted that certain 2-substituents improved enzyme inhibitory potency against genotype 1a NS5B. The combination of optimal substituents at positions 2 and 6 resulted in inhibitors with low nanomolar potencies against genotype 1a/1b NS5B enzymes and the genotype 1b HCV replicon.

Conclusions: Optimization of the 2- and 6-substituents in a series of 5-hydroxy-3(2*H*)-pyridazinones provided NS5B inhibitors with low nanomolar potencies in both biochemical and replicon assays. These inhibitors generally display reasonable solubility properties. Some analogs exhibit very high liver to plasma ratios after oral administration to Sprague–Dawley rats.

doi:10.1016/j.antiviral.2007.01.067

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Synthesis of Novel Types of Anti-Coxsackie Virus Compounds

Michal Šála[1,*], Hubert Hřebabecký[1], Martin Dračínský[1], Armando De Palma[2], Johan Neyts[2], Antonín Holý[1]

[1] Centre for New Antivirals and Antineoplastics, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, 166 10 Prague 6, Czech Republic; [2] Rega Institute for Medical Research, Minderbroedersstraat 10, BE-3000, Leuven, Belgium

We are systematically investigating the series of novel chain-bridged carbocyclic nucleoside derivatives of purine bases. Our synthetic procedure consist of the Mitsunobu reaction of the corresponding alcohols with the purine base, or in the ring closure reaction starting from the previously prepared appropriate amine derivatives. Within this group, we identified several types of novel compounds that exhibit in vitro selective anti-enterovirus activity. The synthesis, detailed SAR study as well as the response of other *Picorna* viruses will be reported.

Acknowledgements: This work is a part of the research project Z4 055 0506. It was supported by the "Centre for New Antivirals and Antineoplastics" (Ministry of Education, Youth and Sports of the Czech Republic, 1M0508), by the NIH grant 1UC1AI062540-01, by the Programme of Targeted Projects of Academy of Sciences of the Czech Republic (1QS400550501). We gratefully acknowledge the financial support of the European Commission (René Descartes Prize-2001 Grant no. HPAW-2002-100096).

doi:10.1016/j.antiviral.2007.01.068

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Metabolism and Pharmacokinetic Studies of SB-9000—A Novel Anti-HBV agent

John Coughlin*, Seetharamaiyer Padmanabhan, Radhakrishnan Iyer

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

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

We have recently reported that certain di-, and tri-nucleoside phosphorothioate (PS) and phosphoramidate (P-NHR) analogs exhibit potent anti-HBV activity in which SB-9000 was identified as a lead dinucleoside phosphorothioate analog.

In vitro studies using mouse and human liver microsomes have revealed that SB-9000 and analogs were metabolically stable for extended periods. The pharmacokinetic profile of di-and tri-nucleotides in rats by IV dosing revealed that it is similar to that of long-chain oligonucleotides—short plasma residence time, and with significant disposition in liver, and kidney and slow elimination.

The pharmacokinetic evaluation of SB-9000 in woodchucks revealed that following the IV administration of SB-9000 at a single dose of 30 mg/kg, the mean plasma C_{max} values of SB-9000 were 49 μg/mL (males) and 37 μg/mL (females). The plasma half-life of the compound was approximately 1 h. SB-9000 was excreted extensively in the urine for up to 24 h at levels between 12 to 840 μg/mL. Importantly, using LC-MS/MS analysis, it was shown that the compound was excreted mostly as unchanged SB-9000. The significant metabolic stability of the compound in woodchucks is similar to that observed in in vitro studies using liver microsomes.

These studies suggest that the anti-HBV activity of SB-9000 is due to the intact dinucleotide structure, and unlikely due to its metabolites or breakdown products. This is in contrast to nucleoside analogs, which require metabolic conversion to the corresponding mono-, di- and tri-phosphates for their antiviral activity.

Acknowledgement: Support of this research from NIH (NIAID) under a Research Project Cooperative Agreement Grant Award 5 UO1 AI058270-03, is gratefully acknowledged.

doi:10.1016/j.antiviral.2007.01.069