Drugs of the Future 2003, 28(9): 870-879

CCC: 0377-8282/2003

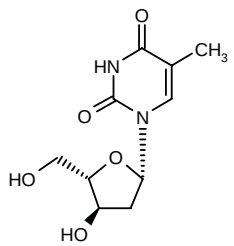
Telbivudine

Anti-HBV Agent

Prop INN; USAN

L-dT
LdT
NV-02B

1-[(2*S*,4*R*,5*S*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione
2'-Deoxy-β-L-thymidine
1-(2-Deoxy-β-L-*erythro*-pentofuranosyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione
1-(2'-Deoxy-β-L-ribofuranosyl)thymine



$C_{10}H_{14}N_2O_5$
Mol wt: 242.2296
CAS: 003424-98-4
EN: 288295

Abstract

Chronic infection with the human hepatitis B virus (HBV) is the ninth most common cause of death worldwide and is considered 50-100 times more contagious than HIV. Treatment of hepatitis B is initiated when infection is considered chronic and the primary goal of therapy is to suppress HBV replication before irreversible liver damage occurs. The standard antiviral treatment for chronic hepatitis B infection is interferon alfa-2b, lamivudine and adefovir dipivoxil. However, drug resistance can develop with long-term treatment, a problem that can be avoided with combination therapy. Research efforts have therefore focused on developing novel direct anti-HBV agents that block HBV replication via inhibition of viral enzymes. From a series of simple "unnatural" nucleosides, telbivudine exhibited potent, selective and specific antiviral activity against HBV replication and was chosen for further development.

Synthesis

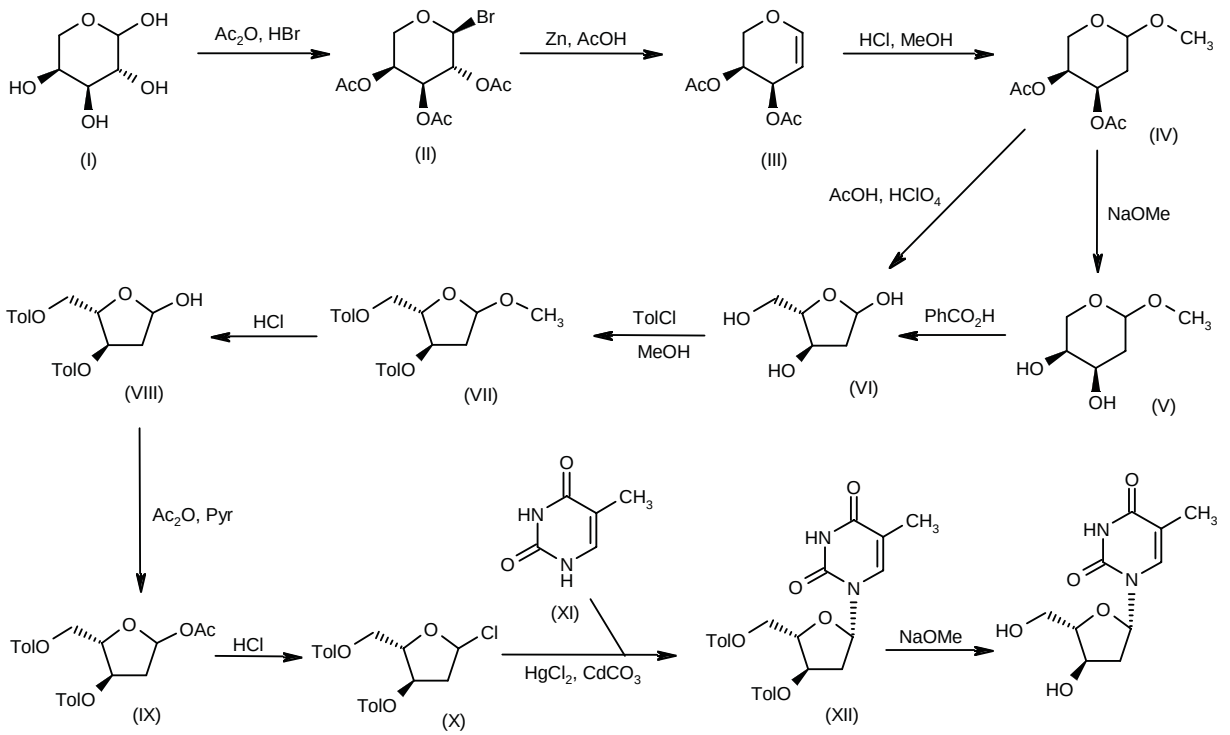
Telbivudine can be prepared by several different ways:

1) The reaction of L-arabinose (I) with acetic anhydride and HBr gives tri-*O*-acetyl-β-L-arabinopyranosyl bromide (II), which is treated with Zn and Cu-Zn couple in aqueous AcOH to yield 3,4-di-*O*-acetyl-L-arabinal (III) (1). Reaction of compound (III) with HCl followed by treatment with refluxing methanol affords methyl 3,4-di-*O*-acetyl-2-deoxy-L-riboside (IV), which is deacetylated by means of NaOMe in methanol to provide methyl 2-deoxy-L-riboside (V). Reaction of riboside (V) with benzoic acid gives 2-deoxy-L-ribofuranose (VI), which, alternatively, can be obtained directly from diacetate (III) by treatment with aqueous $HClO_4$ in AcOH/Ac_2O. Reaction of ribofuranose (VI) with *p*-toluoyl chloride and methanol gives methyl 3,4-di-*O*-toluoyl-2-deoxy-L-riboside (VII), which is demethylated with HCl to yield 3,4-di-*O*-toluoyl-2-deoxy-L-ribose (VIII). Acylation of the ribose (VIII) with Ac_2O and pyridine affords 1-*O*-acetyl-3,4-di-*O*-toluoyl-2-deoxy-L-ribose (IX), which is treated with HCl to provide the chloro-ribose (X). Condensation of compound (X) with thymine (XI) by means of $HgCl_2$ and $CdCO_3$ gives the acylated thymidine (XII), which is finally deacylated by treatment with NaOMe in methanol (2). Scheme 1.

2) 2-Deoxy-L-ribose (VI) is converted into 1-chloro-1,2-dideoxy-3,5-di-*O*-*p*-toluoyl-L-ribose (X) by using Hoffer's method (3) for the D-enantiomer. Treatment of 2-deoxy-L-ribose with MeOH in HCl/MeOH provides methyl 2-deoxy-L-riboside (XIII), which is condensed with *p*-toluoyl chloride by means of $KHCO_3$ in pyridine to give methyl 2-deoxy-3,5-di-*O*-*p*-toluoyl-L-riboside (VII). Chlorination of riboside (VII) with glacial AcOH and HCl affords 1-chloro-1,2-dideoxy-3,5-di-*O*-*p*-toluoyl-L-ribose (X), which is condensed with 5-methyl-2,4-bis(trimethylsilyl-

L.A. Sorbera, J. Castañer, R.M. Castañer, M. Bayés. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Telbivudine

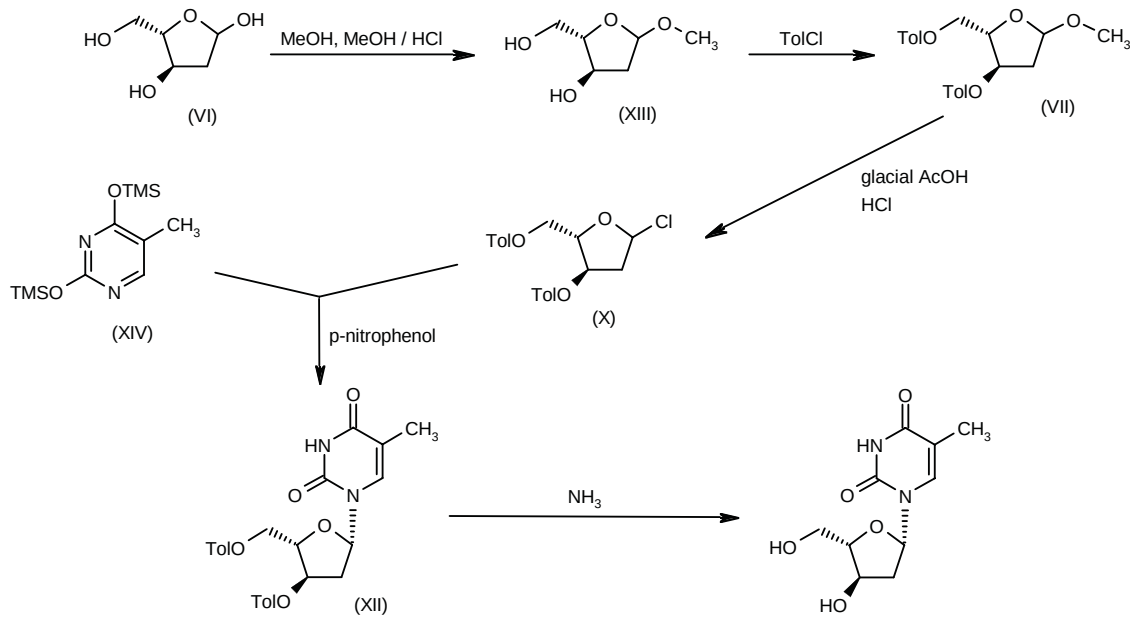


oxy)pyrimidine (XIV) by means of *p*-nitrophenol in chloroform to yield the protected thymidine (XII). Finally, this compound is deprotected by means of NH_3 in methanol (4). Scheme 2.

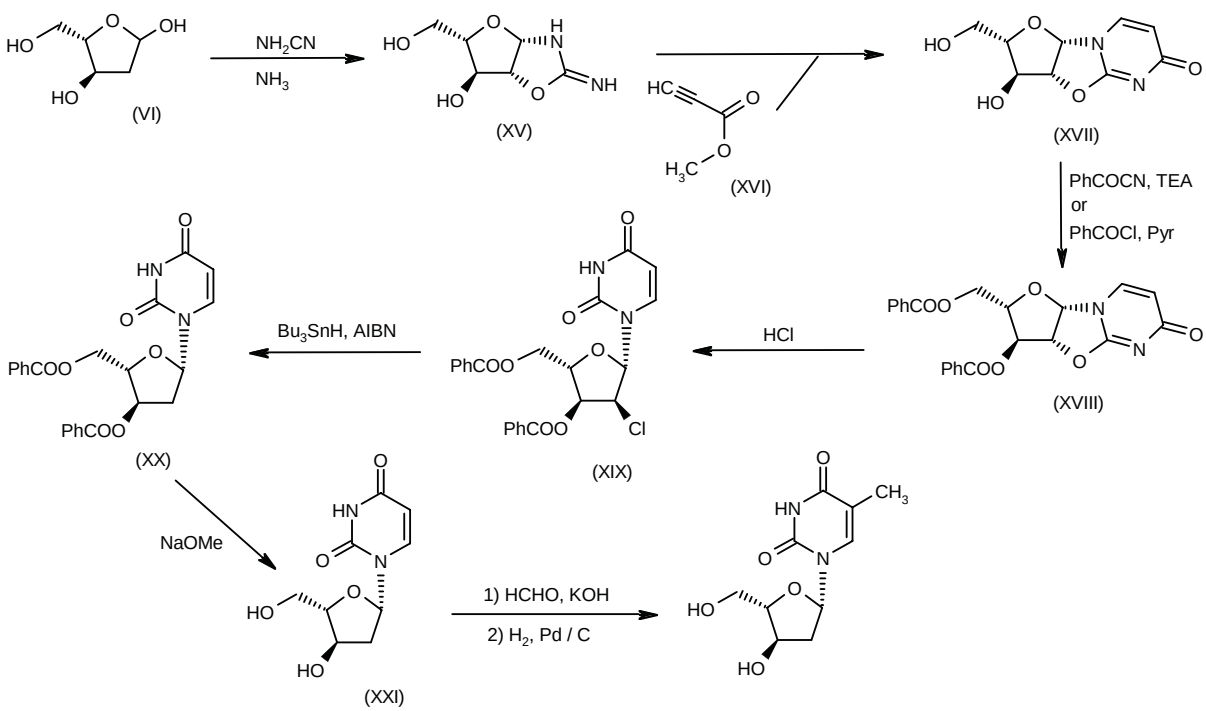
3) Cyclization of L-arabinose (VI) with cyanamide and NH_3 in methanol gives the bicyclic oxazoline (XV), which is submitted to a cycloaddition with methyl propynoate (XVI) in refluxing ethanol/water to yield the tricyclic pyrimidinone system (XVII). Benzoylation of the two OH groups of compound (XVII) with either benzoyl cyanide and triethylamine in DMF (5, 6) or benzoyl chloride in anhydrous pyridine (7) affords the dibenzoate (XVIII), which is treated with HCl in hot DMF to provide the chlorouridine derivative (XIX). Dechlorination of compound (XIX) by means of Bu_3SnH and AIBN in refluxing benzene gives 3,5-di-*O*-benzoyl-2'deoxy-β-L-uridine (XX), which is debenzoylated by means of NaOMe in methanol to yield 2'-deoxy-β-L-uridine (XXI). Finally, this compound is methylated by reaction with formaldehyde and KOH in hot water followed by hydrogenation with H_2 over Pd/C in EtOH/HCl (5-7). Optionally, telbivudine can be purified by benzoylation with benzoyl cyanide and TEA, crystallization in EtOH/ether and final hydrolysis with refluxing MeOH/NaOMe (5). Scheme 3.

4) Reaction of L-xylose (XXII) with acetone and H_2SO_4 gives the acetonide (XXIII), which by acylation with benzoyl chloride in pyridine/chloroform yields the dibenzoate (XXIV). The hydrolysis of acetonide (XXIV) with acetic acid to the dihydroxy sugar (XXV) followed by acylation with acetic anhydride provides the tetracylated L-xylose (XXVI) (8, 9). Condensation of compound (XXVI) with 2,4-bis(trimethylsilyloxy)pyrimidine (XXVII) – obtained by silylation of uracil (XXVIII) with hexamethyldisilazane – by means of trimethylsilyl triflate in 1,2-dichloroethane affords nucleoside (XXIX). Selective hydrolysis of the acetate ester of compound (XXIX) using hydrazine and AcOH in pyridine yields the dibenzoylated xylofuranosyluracil (XXX). Isomerization of compound (XXX) to the arabinofuranosyl analogue (XXXI) is achieved by reaction with dicyclohexylcarbodiimide and dichloroacetic acid in DMSO/benzene, followed by treatment with $NaBH_4$ in EtOH/benzene. Subsequent deoxygenation of the 2'-hydroxyl group of compound (XXXI) to afford 2'-deoxynucleoside (XX) is effected via condensation with phenyl chlorothionoformate, and then reduction of the resulting thiocarbonate (XXXII) with tris(trimethylsilyl)silane and AIBN. Iodination of the uracil ring of (XX) with I_2 and cerium ammonium nitrate (CAN) in acetonitrile produces the 5-iodo derivative (XXXIII), which is protected at the 3-nitrogen atom by condensation with *p*-toluoyl chloride to yield the protected nucleoside (XXXIV). Introduction of the 5-methyl group to give the thymidine derivative

Scheme 2: Synthesis of Telbivudine



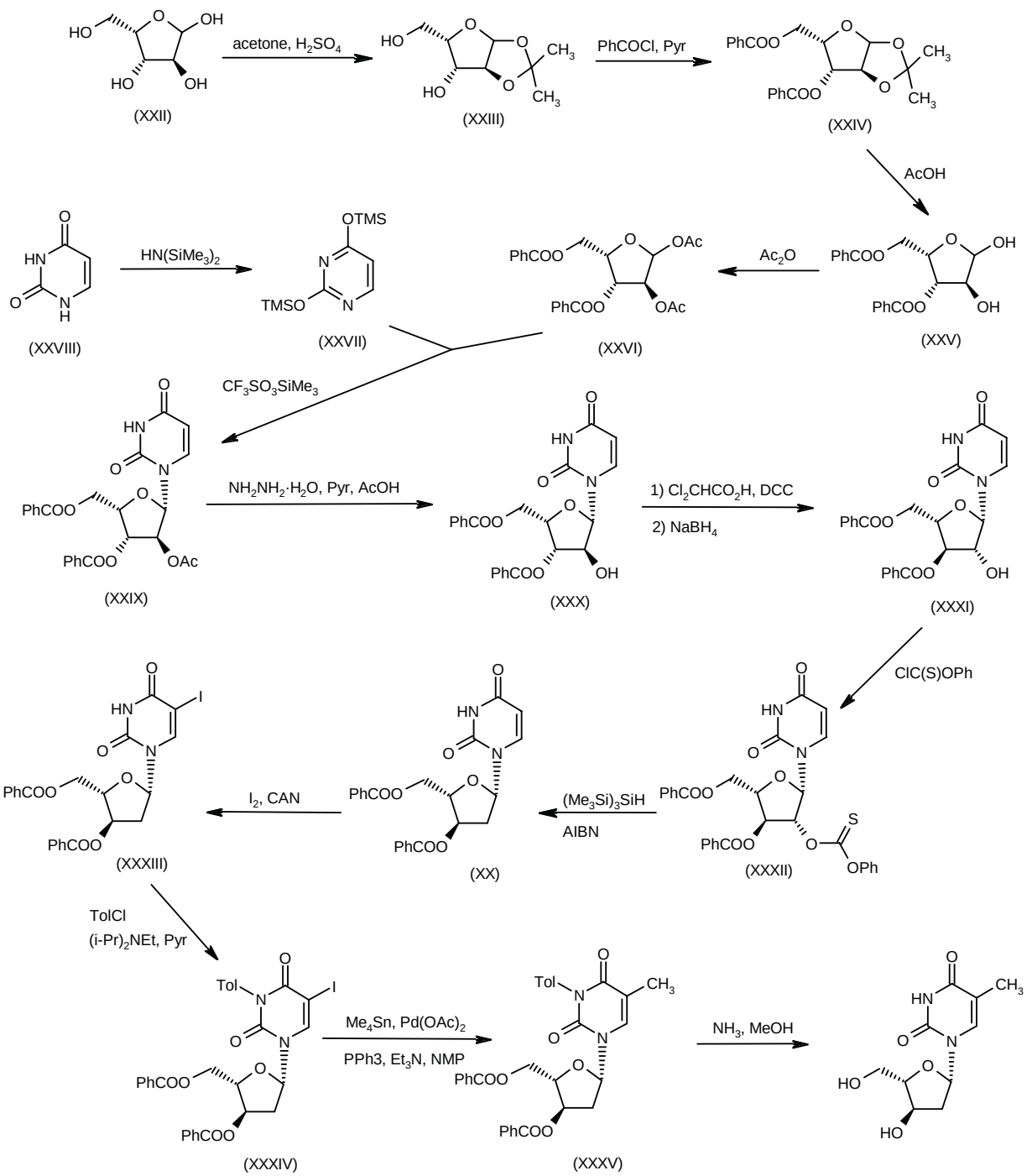
Scheme 3: Synthesis of Telbivudine



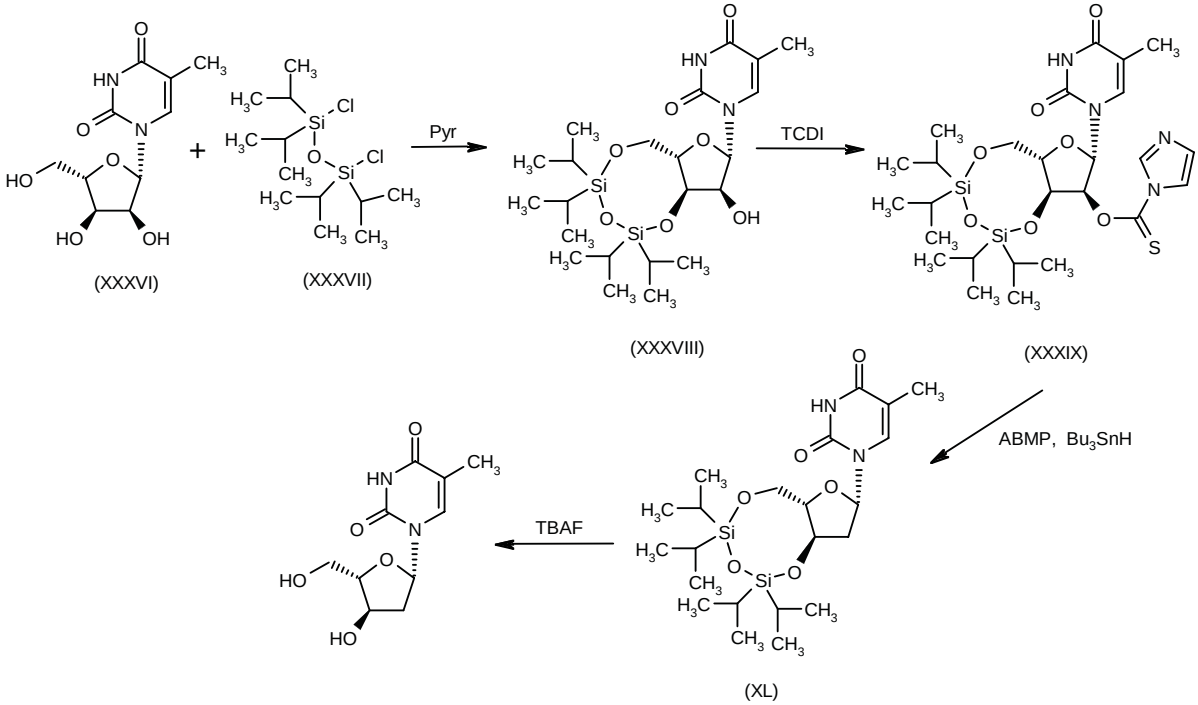
(XXXV) is then effected by reaction of the 5-iodouracil (XXXIV) with tetramethyltin in the presence of palladium catalyst. Finally, all protecting groups of compound (XXXV) are removed by treatment with methanolic ammonia (7). Scheme 4.

5) Condensation of 1-(β-L-ribofuranosyl)thymine (XXXVI) with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (XXXVII) in pyridine gives the cyclic disiloxane nucleoside (XXXVIII), which is acylated with thiocarbonyldiimidazole (TCDI) in DMF to yield the 2'-*O*-thioester derivative

Scheme 4: Synthesis of Telbivudine



Scheme 5: Synthesis of Telbivudine



(XXXIX). Reduction of this compound by means of 2,2'-azobis(methylpropionitrile) (ABMP) and Bu_3SnH in refluxing toluene affords the silylated 2'-deoxynucleoside (XL), which is finally desilylated by means of TBAF in THF (10). Scheme 5.

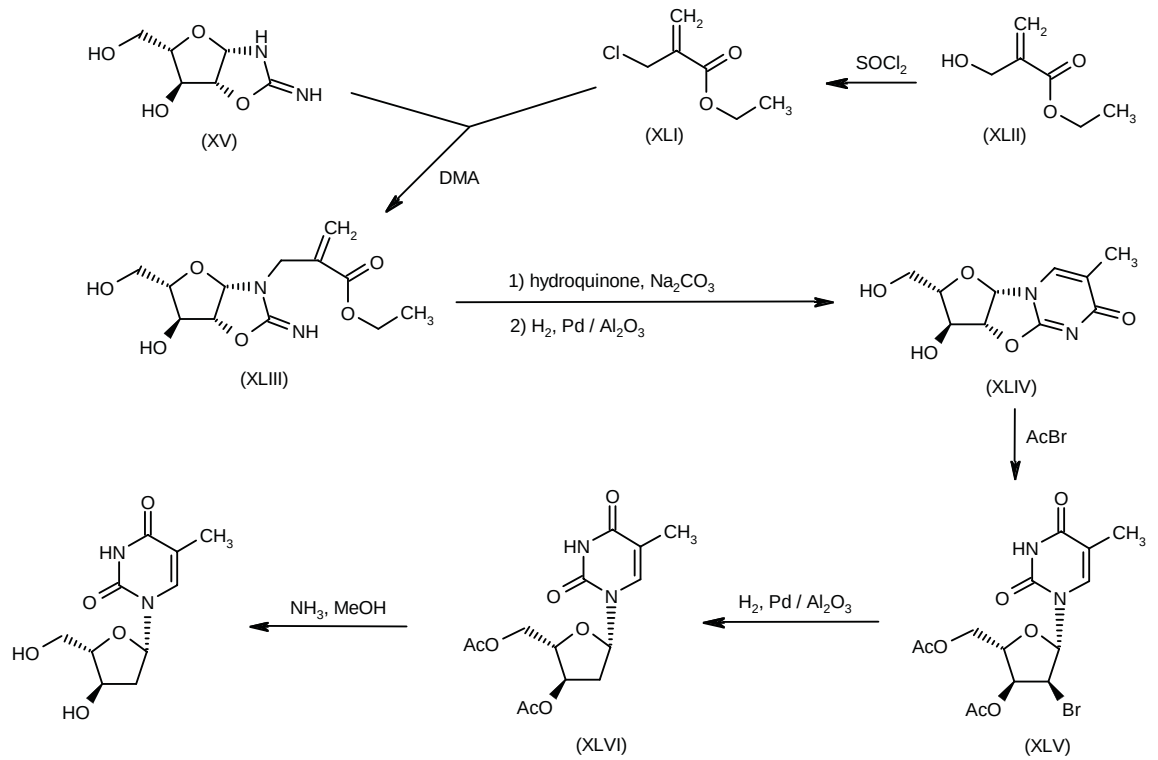
6) Condensation of the bicyclic oxazoline (XV) with 2-(chloromethyl)acrylic acid ethyl ester (XLI) – obtained by treatment of the hydroxymethyl analogue (XLII) with $SOCl_2$ – in dimethylacetamide gives the aduct (XLIII), which is treated first with hydroquinone and Na_2CO_3 in water and then with H_2 over Pd/Al_2O_3 in the same solvent to provide 2,2'-anhydro-β-L-thymidine (XLIV). Reaction of compound (XLIV) with acetyl bromide in DMF/AcOEt yields 2'-bromo-3',5'-di-*O*-acetyl-β-L-thymidine (XLV), which is debrominated with H_2 over Pd/Al_2O_3.to afford the 2'-deoxynucleoside (XLVI). Finally, this compound is deacetylated by means of NH_3 in MeOH (11). Scheme 6.

7) The oxidative cleavage of 1,2,5,6-di-*O*-isopropylidene-D-galactofuranose (XLVII) with $NaIO_4$ and H_5IO_6 gives aldehyde (XLVIII), which is reduced with $NaBH_4$ in methanol to yield the 1,2-di-*O*-isopropylidene-L-arabinose (XLIX). Protection of the OH groups of compound (XLIX) with benzyl chloride and KOH in refluxing dioxane affords the dibenzyl ether (L), which is submitted to cleavage of the acetonide group by means of HCl in methanol to provide the methyl dibenzyl-L-arabinoside (LI). Reaction of the free OH group of (LI) with triflic anhydride and pyridine in dichloromethane gives the triflate (LII), which is reduced with Bu_4NBH_4 in refluxing benzene to yield methyl 3,5-di-*O*-benzyl-2-deoxy-L-riboside (LIII). Debenzylation of (LIII) wit H_2 over Pd/C affords methyl 2-deoxy-L-riboside (LIV), which is finally treated with Dowex [H^+] in hot water to provide the telbivudine intermediate 2-deoxy-L-ribose (VI) (12). Scheme 7.

Introduction

Chronic infection with the human hepatitis B virus (HBV), a partially double-stranded, circular enveloped DNA virus belonging to the Hepadnaviridae family, is the ninth most common cause of death worldwide. It is estimated that hepatitis B-relaated disease causes 1-2 million deaths per year worldwide. HBV replicates mainly in hepatocytes via reverse transcription of an RNA-replicative intermediate. Replication of HBV is only mildly cytotoxic toward the host cell. However, the cellular immune response from HBV-induced liver damage is the cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. HBV is transmitted by percutaneous or permucosal exposure to infected body fluids including sexual contact with an infected person or perinatal transmission. It can also be transmitted in settings where there is continuous close personal contact (*i.e.*, among family members). The World Health Organization (WHO) considers HBV to be 50-100 times more contagious than HIV (13).

Scheme 6: Synthesis of Telbivudine

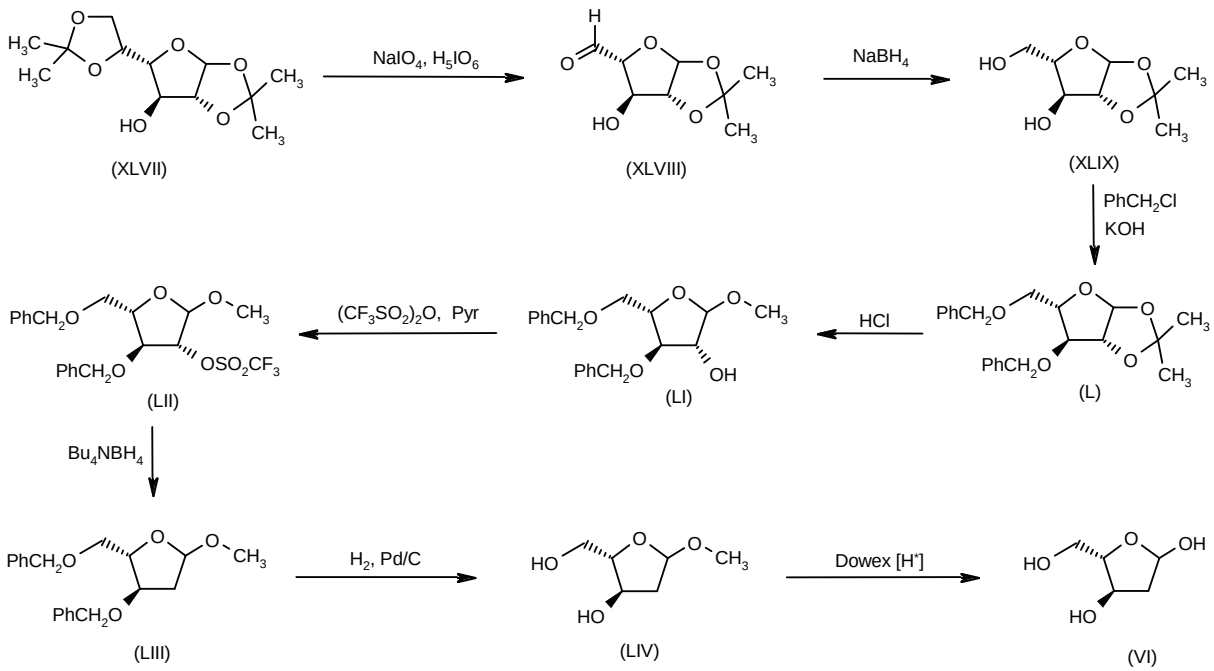


There are an estimated 350 million carriers of HBV worldwide, with nearly one-third expected to develop progressive liver disease. Acute infection ranges in severity from asymptomatic to fulminant hepatitis. The most serious complication of acute infection is fulminant liver failure which occurs in fewer than 1% of all patients. Most (90-95%) acutely infected patients recover completely with only 0.1-1% dying from fulminant hepatitis and 5-10% becoming chronic carriers of the virus. Chronic infection is diagnosed when the presence of HBV surface antigen (HBsAg) can be detected in serum for at least 6 months. Intermittent fatigue which is usually mild is the most common symptom of chronic HBV infection, although most patients are asymptomatic. Signs of liver disease are only seen when a patient progresses to clinically apparent cirrhosis (13).

Treatment of hepatitis B is initiated when infection is considered chronic and the patient's alanine aminotransferase (ALT) levels are 2-fold higher than normal and tests for HBV DNA and for hepatitis e antigen (HBeAg) are positive (13, 14). The primary goal of treatment to suppress HBV replication before irreversible liver damage occurs. The standard antiviral treatment for chronic hepatitis B infection is interferon alfa-2b, lamivudine and adefovir dipivoxil. However, a major problem with long-term (more than 12 months) treatment with agents such as lamivudine is that drug resistance can develop. Lamivudine-resistant hepatitis B is characterized by amino acid site mutations in the YMDD locus of the catalytic domain of HBV polymerase. Drug resistance could be avoided with combination therapy such as treatment with lamivudine or interferon together with other antiviral agents. Thus, research efforts have focused on developing novel direct anti-HBV agents that block HBV replication via inhibition of polymerase, reverse transcriptase or other viral enzymes.

A series (known collectively as Novirio NV-02) of simple "unnatural" nucleosides have been discovered that selectively inhibit HBV replication. Unlike other nucleoside analogues present in the clinic, these molecules are not chemically modified. The molecules closely resemble natural deoxynucleosides, differing only with respect to the spatial relationship of their base and sugar moieties so that they have a L-configuration as opposed to the D-configuration seen in the natural deoxynucleosides. These β-L-nucleosides include β-L-2'-deoxycytidine (L-dC), β-L-2'-deoxyadenosine (L-dA) and β-L-thymidine (L-dT; NV-02B; telbivudine), and their specific antihepadnavirus activity was shown to be conferred by the 3'-OH group of the β-L-2'-deoxyribose sugar. Telbivudine, in particular, exhibited potent, selective and specific antiviral activity against HBV replication, with no effects on human

Scheme 7: Synthesis of Intermediate (VI)



DNA polymerases. Telbivudine was chosen for further development as a treatment for chronic hepatitis B (15, 16).

Pharmacological Actions

Telbivudine potently and selectively inhibited HBV in a human hepatoma cell line (2.2.15), with little effects observed on HIV-1(LAI) infected human peripheral blood mononuclear cells (PBMCs) (EC_{50} = 0.19 ± 0.09 μM *vs.* > 200 μM). The agent, at concentrations up to 100 μM, had no inhibitory effects on human DNA polymerases α, β or γ or cytotoxic effects (50% cytotoxic concentration [CC_{50}] > 1000 μM) on 2.2.15 cells, primary human PBMCs, human foreskin fibroblasts or human bone marrow progenitor cells. The agent also had no effect on mitochondrial function or morphology in experiments using HepG2 cells. It has been suggested that telbivudine inhibits HBV replication through inhibition of the reverse transcription of HBV pregenomic RNA (15).

Telbivudine was also shown to have further selectivity *in vitro* by potently inhibiting woodchuck hepatitis virus (WHV) and duck HBV (DHBV) replication (EC_{50} = 0.05 μM or less) but having no effect on HIV, respiratory syncytial virus (RSV), herpes simplex virus (HSV), varicella zoster virus (VZV), human cytomegalovirus (HCMV), Epstein Barr virus (EBV), measles virus, adenovirus, rhinovirus, influenza and parainfluenza virus replication (17).

In vitro experiments using HepG2 49-27 cells stably expressing wild-type HBV determined that 1-week treatment with adefovir dipivoxil in combination with telbivudine, lamivudine or entecavir resulted in additive inhibition of viral replication. No significant synergy or antagonism were observed (18).

The activity of telbivudine against lamivudine-resistant HBV was examined *in vitro* in experiments using HepG2 cells transfected with wild-type HBV or rtL180M, rtM204I or rtL180M + rtM204V mutant HBV. Results showed that lamivudine-resistant HBV are cross-resistant to telbivudine. Telbivudine inhibited replication of wild-type HBV (IC_{50} = 0.25 μM) but the rtL180M mutation conferred an approximate 10-fold resistance. High levels of resistance (more then 300-fold) were observed for the rtM204I and rtL180M + rtM204V mutations (19).

The cross-resistance of telbivudine, adefovir and entecavir were examined in *in vitro* experiments using HepG2 cells expressing wild-type HBV or the drug-resistant HBV mutants L528M, M552I or L528M + M552V. Telbivudine inhibited wild-type replication with an IC_{50} value of 0.17 μM. However, the M552I and L528M + M552V polymerase mutations conferred cross-resistance to the agent (235- and 132-fold, respectively); cross-resistance to telbivudine was also observed in cells expressing the L528M mutation alone (10-fold) which was

similar to the resistance conferred to lamivudine. High resistance to lamivudine (> 1000-fold) was seen in cells expressing the M552I and L528M + M552V mutations. Entecavir was active against wild-type HBV (IC_{50} = 0.0022 μM) but was 860- and 180-fold less effective against the lamivudine resistant mutants M552I and L528M + M552V, respectively. Adefovir retained efficacy against all mutants (IC_{50} values within 3.7-fold of wild-type) (20).

The *in vivo* activity of telbivudine (0.01, 0.1, 1 and 10 mg/kg p.o. once daily for 28 days) was examined and compared to lamivudine (10 mg/kg/day) in a woodchuck model of chronic HBV infection. Significant inhibition in WHV DNA replication was observed within the first day of treatment with telbivudine. At day 14, plasma viral load decreased to below the detection limit in animals treated with the 10 mg/kg dose of telbivudine; decreases of as much as 8 log from baseline were observed by days 14-28. Moreover, a delay of 2-4 weeks was observed in posttreatment viral rebound in these animals. Lamivudine was less effective, with decreases in serum viral load of only 0.5 log; this was concluded to be due to the low administered dose (15, 21).

Similar results were obtained in a 12-week study using the woodchuck model of chronic HBV infection. In this study, animals were treated with a combination of telbivudine and L-dC (1 mg/kg/day p.o.). A decrease in plasma viral load of 8 log or more and a parallel marked reduction in HBsAg were seen in treated animals. No toxicities were observed with treatment (22).

The toxicity of acute and repeated dosing (4 weeks) with oral telbivudine (up to 2000 mg/kg/day) was examined in rats and cynomolgus monkeys. No significant toxicities were noted with acute or repeated doses in either species, including no effects on body weight, food consumption, hematology, organ weight or histopathology. The no observed adverse events level was concluded to be 2000 mg/kg. Administration of doses up to 2000 mg/kg also had no effects on male or female mice. The agent at concentrations up to 5000 μg/plate was nonmutagenic in *Salmonella* or *Escherichia coli* plate mutation assays. Moreover, no clastogenic effects were noted in CHO cell chromosome aberration assays (23).

Pharmacokinetics and Metabolism

An HPLC method has been described to determine telbivudine in human plasma. The method had a quantitation limit of 0.1 μg/ml and recovery from human plasma ranged from 74.5-94.1% (mean recovery = 90.6%) (24).

The pharmacokinetics of i.v. and oral telbivudine (10 mg/kg) were examined in cynomolgus monkeys and woodchucks. Plasma levels of the agent decreased biexponentially following i.v. administration; levels were undetectable after 8 h. The terminal $t_{1/2}$ values were about 1.5 h and 3.5 h in monkeys and woodchucks, respectively, and total clearance was higher in monkeys (about 0.60 *vs.* 0.30 l/h/kg). Similar good tissue distribution was observed for both species. Absorption was slow following oral dosing in both species (C_{max} occurred 1-4 h post-dosing). Absolute bioavailability was calculated to be 68.6% and 38.3% in monkeys and woodchucks, respectively (16).

The intracellular metabolism of telbivudine was examined in HepG2 cells and primary cultured human hepatocytes. The agent was extensively phosphorylated in both cell types to telbivudine monophosphate, telbivudine diphosphate and its major metabolite, the 5'-triphosphate derivative (L-dTTP). L-dTTP levels were 27.7 ± 12.1 and 16.5 ± 9.8 pmol/10 million cells in HepG2 and human hepatocytes, respectively. The intracellular half-life for L-dTTP was at least 15 h. Intracellular concentrations of L-dTTP remained at levels equivalent to IC_{50} values for WHV DNA polymerase (about 0.24 μM) for 24 h after drug removal. Experiments using human and woodchuck liver extracts showed that telbivudine was phosphorylated by thymidine kinase (21, 25).

Clinical Studies

The safety and efficacy of telbivudine (25, 50, 100, 200 and 400 mg p.o. once daily for 28 days with a 12-week follow up) were shown in a phase I/II, blinded dose escalation trial conducted in patients with chronic HBV infection. To date, 24 patients have completed treatment and the 400 mg cohort continues. All doses resulted in a greater than 99% reduction in serum viral load within 4 weeks. Total mean reductions in HBV DNA at 4 weeks were 2.4 ± 0.3, 2.7 ± 0.2, 3.1 ± 0.1 and 2.9 ± 0.2 log_{10} for cohorts dosed with 25, 50, 100 and 200 mg/day, respectively; preliminary results from the 400 g/day cohort indicated viral load reductions of 3.6 log_{10} by week 4. No significant toxicities were reported. Second phase HBV clearance (weeks 2-4) was dose-proportional and posttreatment increases in HBV DNA were slower in the higher dose groups. There was no clear dose-proportionality in overall HBV suppression for doses higher than 25 mg. However, viral dynamics modeling predicted that higher doses (600-800 mg/day) or longer treatment may cause 6-7 log_{10} reductions in HBV DNA. (26-28) (Table I).

A multicenter, randomized, blinded, ongoing phase IIb trial conducted in 104 patients with chronic HBV infection compared the safety and efficacy of treatment with oral telbivudine (400 or 600 mg/day) or lamivudine (100 mg/day) alone or in combination for 52 weeks. Thirty patients were evaluable at 12 weeks. At weeks 1 and 12, respectively, HBV DNA reductions were (mean reduction from baseline in log_{10} copies/ml): 2.27 ± 0.1 and 3.87 ± 0.4 with lamivudine alone, 2.44 ± 0.3 and 4.34 ± 0.3 with 400 mg telbivudine, 2.15 ± 0.3 and 4.64 ± 0.6 with 600 mg telbivudine, 2.38 ± 0.2 and 4.97 ± 0.6 with 400 mg telbivudine + lamivudine and 2.80 ± 0.3 and 4.64 ± 0.6 with 600 mg telbivudine + lamivudine. Reductions in HBV DNA seen between week 4 and 12 were less for patients treated with lamivudine alone as compared to

Table I: Clinical studies of telbivudine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis B	Double-blind	Telbivudine, 25 mg od x 28 d (n=6) Telbivudine, 50 mg od x 28 d (n=6) Telbivudine, 100 mg od x 28 d (n=6) Telbivudine, 200 mg od x 28 d (n=6)	24	Telbivudine at doses ranging from 25-200 mg/day was safe and reduced viral DNA by more than 99% in patients with chronic hepatitis B. The higher doses were associated with a slower return of viral DNA levels to baseline after completing treatment	26-28
Hepatitis B	Randomized, double-blind, multicenter	Telbivudine, 400 mg od x 12 wk Telbivudine, 600 mg od x 12 wk Lamivudine, 100 mg od x 12 wk Telbivudine, 400 mg od + Lamivudine, 100 mg od x 12 wk Telbivudine, 600 mg od + Lamivudine, 100 mg od x 12 wk	104	Telbivudine alone or combined with lamivudine was more effective than lamivudine alone in reducing the serum levels of viral DNA in patients with hepatitis B	29

patients treated with a regimen including telbivudine (0.21 ± 0.1 *vs.* 1.25 ± 0.17 $\log_{10}$). In addition, more patients treated with telbivudine alone or in combination had HBV viremia reduced to levels below 5 (76 *vs.* 40%), below 4 (52 *vs.* 20%) and below 3 $\log_{10}$ (24 *vs.* 0%) as compared to patients treated with lamivudine alone. Preliminary results from all patients at week 24 showed that ALT levels were normalized in 75% of the patients receiving telbivudine monotherapy. Treatment was well tolerated with no treatment-related or dose-limiting adverse events reported. It was concluded that telbivudine-containing arms had better antiviral effects as compared to lamivudine alone. Final results at 52 weeks are expected in the Fall of 2003 (29-31).

A multicenter phase III study of telbivudine in approximately 1200 patients is currently under way. The study will examine the safety and efficacy of telbivudine as compared to standard treatment in patients with HBeAg-positive and HBeAg-negative compensated liver disease. The safety and efficacy of telbivudine is also being studied as a treatment for HBV infection in naive adult patients coinfected with HBV and HIV. Telbivudine alone and in combination with a lamivudine-base HAART regimen will be examined (31).

Source

Developed by Idenix Pharmaceuticals Ltd. (US) (formerly Novirio Pharmaceuticals Ltd.); licensed to Sumitomo Pharmaceuticals Co., Ltd. (JP) for Japan, South Korea, Taiwan and China and to Novartis AG (CH) for the rest of the world.

References

1. Humoller, F.L. *L-Ribose. Oxidation of L-arabinal.* Methods Carbohydr Chem 1962: 83-8.

2. Smejkal, J., Sorm, F. *Nucleic acids components and their analogues. LIII. Preparation of 1-2'-deoxy-β-L-ribofuranosylthymine, "L-thymidine".* Coll Czech Chem Commun 1964, 29: 2809-13.

3. Hoffer, M. *α-Thymidine.* Chem Ber 1960, 93: 2777-81.

4. Fujimori, S., Iwanami, N., Hashimoto, Y., Shudo, K. *A convenient and stereoselective synthesis of 2'-deoxy-β-L-ribonucleosides.* Nucleosides Nucleotides 1992, 11: 341-9.

5. Holý, A. *Nucleic acid components and their analogues. CLIII. Preparation of 2'-deoxy-L-ribonucleosides of the pyrimidine series.* Coll Czech Chem Commun 1972, 37: 4072-87.

6. Weis, A.L., Goodhue, C.T., Shanmuganathan, K. (Genencor International, Inc.; Lipitek, Inc.). *L-Ribofuranosyl nucleosides.* WO 9613512.

7. Gosselin, G., Imbach, J.-L., Bryant, M.L. (Idenix Pharmaceuticals Ltd.; CNRS [Centre National de la Recherche Scientifique]). *β-L-2'-Deoxy-nucleosides for the treatment of hepatitis B.* EP 1104436, JP 2002522552, US 6395716, WO 0009531.

8. Gosselin, G., Imbach, J.-L., Aubertin, A.-M., Sommadossi, J.-P., Schinazi, R.F. (CNRS [Centre National de la Recherche Scientifique]). *2' or 3'-Deoxy and 2'-dideoxy-β-L-pentafuranonucleoside cpds., method of preparation and application in therapy, especially as anti-viral agents.* DE 2709754, EP 0717748, WO 9507287.

9. Gosselin, G., Bergogne, M.C., Imbach, J.L. *Synthesis and antiviral evaluation of β-L-xylo-furanosyl nucleosides of the five naturally occurring nucleic acid bases.* J Heterocycl Chem 1993, 30: 1229-33.

10. Watanabe, K.A., Choi, W.-B. (Pharmasset Ltd.). *Synthesis of 2'-deoxy-L-nucleosides.* WO 0134618.

11. Iizuka, H., Togashi, K., Suzuki, T. (Mitsui Chemicals, Inc.). *L-Nucleic acid derivs. and processes for the synthesis thereof.* EP 1348712, JP 2002241390, WO 0244194.

12. Shi, Z.-D., Yang, B.-H., Wu, Y.-L. *A stereospecific synthesis of L-deoxyriboside, L-riboside and L-ribosides.* Tetrahedron 2002, 58: 3287-96.

13. Prous Science Drug R&D Backgrounders: *Hepatitis B (online publication).* Updated August 11, 2003.

14. Colgan, R., Michocki, R., Greisman, L., Moore, T.A. *Antiviral drugs in the immunocompetent host: Part I. Treatment of hepatitis, cytomegalovirus, and herpes infections.* Am Fam Physician 2003, 67: 757-62.

15. Bryant, M.L., Bridges, E.G., Placidi, L. et al. *Antiviral L-nucleosides specific for hepatitis B virus infection.* Antimicrob Agents Chemother 2001, 45: 229-35.

16. Standring, D.N., Bridges, E.G., Placidi, L. et al. *Antiviral β-L-nucleosides specific for hepatitis B virus infection.* Antivir Chem Chemother 2001, 12(Suppl. 1): 119-29.

17. Sommadossi, J.-P., Bryant, M.L., Gosselin, G., Schinazi, R.F., Imbach, J.-L. *Anti-hepatitis B specific β-L-2'-deoxynucleosides.* J Gastroenterol Hepatol 2001, 16: A12.

18. Delaney, W., Yang, H., Miller, M., Gibbs, C., Xiong, S. *Combinations of adefovir with lamivudine, entecavir, or L-dT produce additive antiviral effects against HBV in vitro.* J Hepatol 2002, 36(Suppl. 1): Abst 67.

19. Delaney, W., Yang, H., Miller, M., Gibbs, C., Xiong, S. *Lamivudine-resistant HBV is cross-resistant to L-dT and dC in vitro.* J Hepatol 2002, 36(Suppl. 1): Abst 309.

20. Delaney, W.E. IV, Yang, H., Westland, C.E., Lin, K.-Y., Miller, M.D., Gibbs, C.S., Xiong, S. *In vitro cross-resistance testing of adefovir, entecavir, and β-L-thymidine (L-dT) against drug-resistant strains of HBV*. Hepatology 2001, 34(4, Part 2): Abst 1825.

21. Bridges, E.G., Juodawlkis, A., Faraj, A. et al. *Antiviral activity of β-L-thymidine and β-L-deoxycytidine in the woodchuck model of chronic hepatitis B infection.* Antivir Res 2000, 46(1): Abst 91.

22. Juodawlkis, A., Bridges, E., Cretton-Scott, E. et al. *Synergistic antiviral L-nucleosides specific for hepatitis B virus infection.* Antivir Res 2001, 50(1): Abst 14.

23. Bridges, E.G., Juodawlkis, A., Gosselin, G., Imbach, J.-L., Sommadossi, J.-P., Bryant, M. *Toxicological evaluation of the anti-HBV agent β-L-deoxythymidine.* Antivir Res 2001, 50(1): Abst 146.

24. Lai, K.S. *Determination of β-L-thymidine (L-dT; NV-02B) in human plasma by high performance liquid chromatography*. Clin Chem 2001, 47(6, Suppl.): Abst 215.

25. Hernandez-Santiago, B., Placidi, L., Cretton-Scott, E. et al. *Pharmacology of β-L-thymidine and β-L-2'-deoxycytidine in HepG2 cells and primary human hepatocytes: Relevance to chemotherapeutic efficacy against hepatitis B virus.* Antimicrob Agents Chemother 2002, 46: 1728-33.

26. Lai, C.-L., Myers, M.W., Pow, D.M., Brown, N.A., Lee, Y.-M., Yen, M.-F.m Lim, S.G. *Safe and potent suppression of hepatitis B virus (HBV) with L-deoxythymidine (LDT): Results of a dose-escalation trial.* Hepatology 2001, 34(4, Part 2): Abst 597.

27. Zhou, X.-J., Lim, S.G., Brown, N.A., Myers, M.W., Pow, D.M., Lai, C.-L. *Importance of second-phase HBV clearance and viral dynamic modeling for dose optimization of hepatitis B antiviral nucleosides.* Hepatology 2001, 34(4, Part 2): Abst 607.

28. Zhou, X.-J., Lai, C.-L., Brown, N., Myers, M., Pow, D., Lim, S.-G. *Dose optimization for LdT and other hepatitis B antivirals: Importance of second-phase clearance and viral dynamics modeling.* 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst H-464.

29. Lai, C.-L., Leung, N., Teo, E.K. et al. *International multicenter trial of LdT (telbivudine) alone or in combination with lamivudine, for chronic hepatitis B: An interim analysis.* 53rd Annu Meet Am Assoc Study Liver Dis (Nov 1-5, Boston) 2002, Abst 554.

30. *Idenix reports positive results for NM-283 and telbivudine.* DailyDrugNews.com (Daily Essentials) April 16, 2003.

31. *Hepatitis B.* Idenix Web Site June 16, 2003.

Additional References

Bryant, M.L., Gosselin, G., Schinazi, R.F., Imbach, J.-L., Sommadossi, J.-P. *Anti-hepatitis B specific β-L-2'-deoxynucleosides.* Antivir Res 2000, 46(1): Abst 67.

Placidi, L., Hernández, B., Cretton-Scott, E., Faraj, A., Bryant, M., Imbach, J.-L., Gosselin, G., Pierra, C., Dukhan, D., Sommadossi, J.-P. *Cellular pharmacology of β-L-thymidine (L-dT, NV-02B) and β-L-2'-deoxycytidine (L-dC, NV-02C) in HepG2 cells and primary rat, monkey and human hepatocytes.* Antivir Res 2000, 46(1): Abst 70.

Faraj, A., Loi, A.G., Cui, L. et al. *β-L-Thymidine and β-L-2'-deoxycytidine are potent, selective and specific anti-hepatitis B virus agents.* Antivir Res 2000, 46(1): Abst 88.

Pierra, C., Dukhan, D., Bryant, M., Sommadossi, J.-P., Imbach, J.-L., Gosselin, G. *β-L-2'-Deoxynucleosides as potent anti-HBV agents (Part II): Large-scale stereospecific syntheses of β-L-2'-deoxycytidine and β-L-thymidine.* Antivir Res 2000, 46(1): Abst 90.

Lai, C.L., Lim, S.G., Yuen, M.F., Pow, D.M., Myers, M.W. *L-dT: An ongoing phase I/II dose escalation trial in patients with chronic HBV infection (NV-02B-001).* J Hepatol 2001, 34(Suppl. 1): 139.

Lim, S.G., Lai, C.-L., Lee, Y.-M., Pow, D.M., Myers, M.W. *L-dT: An ongoing phase I/IIa dose-escalation trial in patients with chronic HBV infection (NV-02B-001).* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2907.

Delaney, W.E. IV, Locarnini, S., Shaw, T. *Resistance of hepatitis B virus to antiviral drugs: Current aspects and directions for future investigation.* Antivir Chem Chemother 2001, 12: 1-35.

Chong, Y., Chu, C.K. *Molecular modeling studies of HBV DNA polymerase with anti-HBV L-nucleosides.* 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 242.