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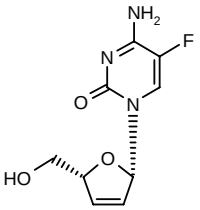
CCC: 0377-8282/2002

ACH-126443

Anti-HBV
Anti-HIV

L-D4FC
β-L-Fd4C

β-L-2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine



$C_9H_{10}FN_3O_3$
Mol wt: 227.194
CAS: 181785-84-2
EN: 236929

Abstract

Chronic hepatitis B virus (HBV) infection is a major global health concern with an estimated 1-2 million individuals dying every year from hepatitis B-related disease. The goal of treatment for chronic HBV infection is to suppress HBV replication prior to development of irreversible liver damage which ideally would be accomplished with antiviral agents and immunomodulatory therapy. Over the past 10 years, research has focused on the development of anti-HBV agents able to directly block HBV replication. Naturally occurring nucleoside analogues were used early to treat hepatitis B with little success or high levels of toxicity. The search for novel nucleoside-based chemotherapies continues through modification of the naturally occurring nucleoside-based agents. Of the new generation nucleoside analogues, lamivudine proved to be a potent and well tolerated inhibitor of HBV replication and is clinically available for the treatment of chronic HBV infection. However, long-term treatment with the agent is associated with the development of drug resistance. ACH-126443 is a novel unnatural L-nucleoside reverse transcriptase inhibitor that has shown potent and selective activity against HBV and has also shown significant efficacy against HIV. Due to its promising potent preclinical profile, ACH-126443 was selected for further development as a treatment for chronic HBV and HIV infections.

Synthesis

ACH-126443 can be prepared by several different ways:

1) Reaction of D-glutamic acid (I) with $NaNO_2$ and HCl gives the lactone carboxylic acid (II), which is esterified with EtOH and TsOH to yield the ester (III), which is reduced with $NaBH_4$ in ethanol and silylated with TBDPS-Cl and imidazole to afford the protected chiral lactone (IV) (1). The selenation of lactone (IV) with *N*-(phenylseleno)phthalimide (V) by means of LiHMDS and TMS-Cl in THF gives a mixture of diastereoisomers with a 3:1 ratio of the desired diastereoisomer (VI). The unwanted isomer (VII) can be isomerized by reaction with DBU in THF. Reduction of the lactone (VI) with DIBAL in toluene affords the lactol (VIII), which is treated with Ac_2O and TEA to provide the acetoxy compound (IX). Condensation of compound (IX) with 5-fluoro-*N*,*O*-bis(trimethylsilyl)cytosine (X) by means of TMS-OTf in dichloromethane gives the selenated cytosine derivative (XI), which is treated with H_2O_2 in THF/pyridine to yield the unsaturated silylated precursor (XII). Finally, this compound is desilylated with HF and TEA in THF (1, 2). Scheme 1.

2) Reaction of L-arabinose (XIII) with cyanamide (XIV) in aqueous methanolic ammonia gives the oxazolidine derivative (XV), which is cyclized with methyl propynoate (XVI) in refluxing ethanol to yield the anhydro uridine (XVII). Acylation of both OH groups of (XVII) by means of benzoyl cyanide (XVIII) in DMF affords the dibenzoate (XIX), which is treated with anhydrous HCl in DMF to provide the chloro uridine derivative (XX) or with HI in DMF or LiI and BH_3/Et_2O in DMF to provide the iodo uridine (XXI). Dehalogenation of (XX) or (XXI) by means of tributyltin hydride in refluxing benzene furnishes 3',5'-di-*O*-benzoyl-2'-deoxy-β-L-uridine (XXII) (3). The *trans*-glycosylation of (XXII) with bis(trimethylsilyl)-5-fluorouracil (XXIII) by means of TMS-OTf in acetonitrile gives the corresponding 5-fluoro-L-uridine derivative (XXIV) as a mixture of the α- and β-anomers that is separated by chromatography. Debenzoylation of (XXIV) with ammonia in methanol yields 2'-deoxy-β-L-uridine (XXV) (4), which is

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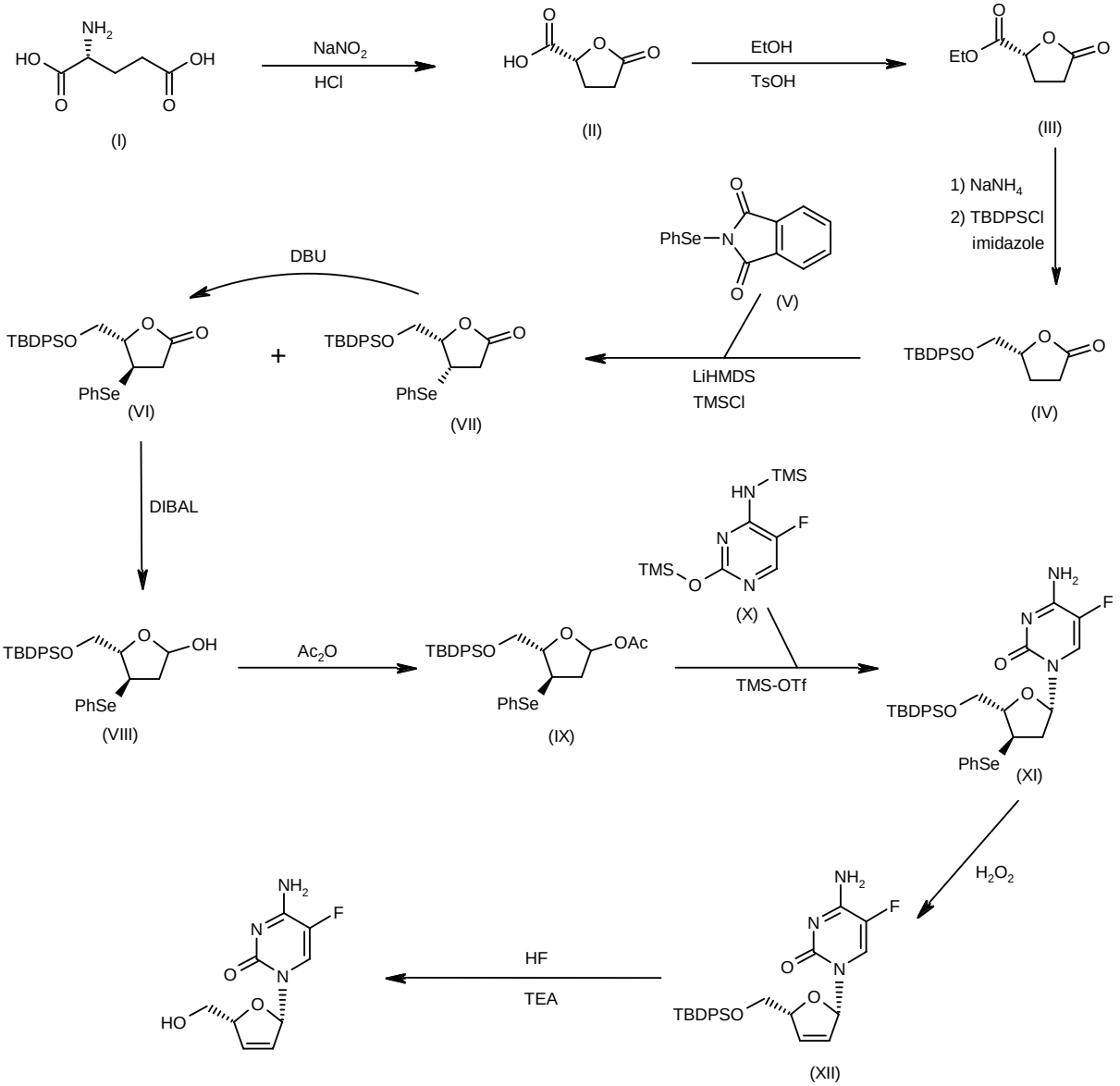
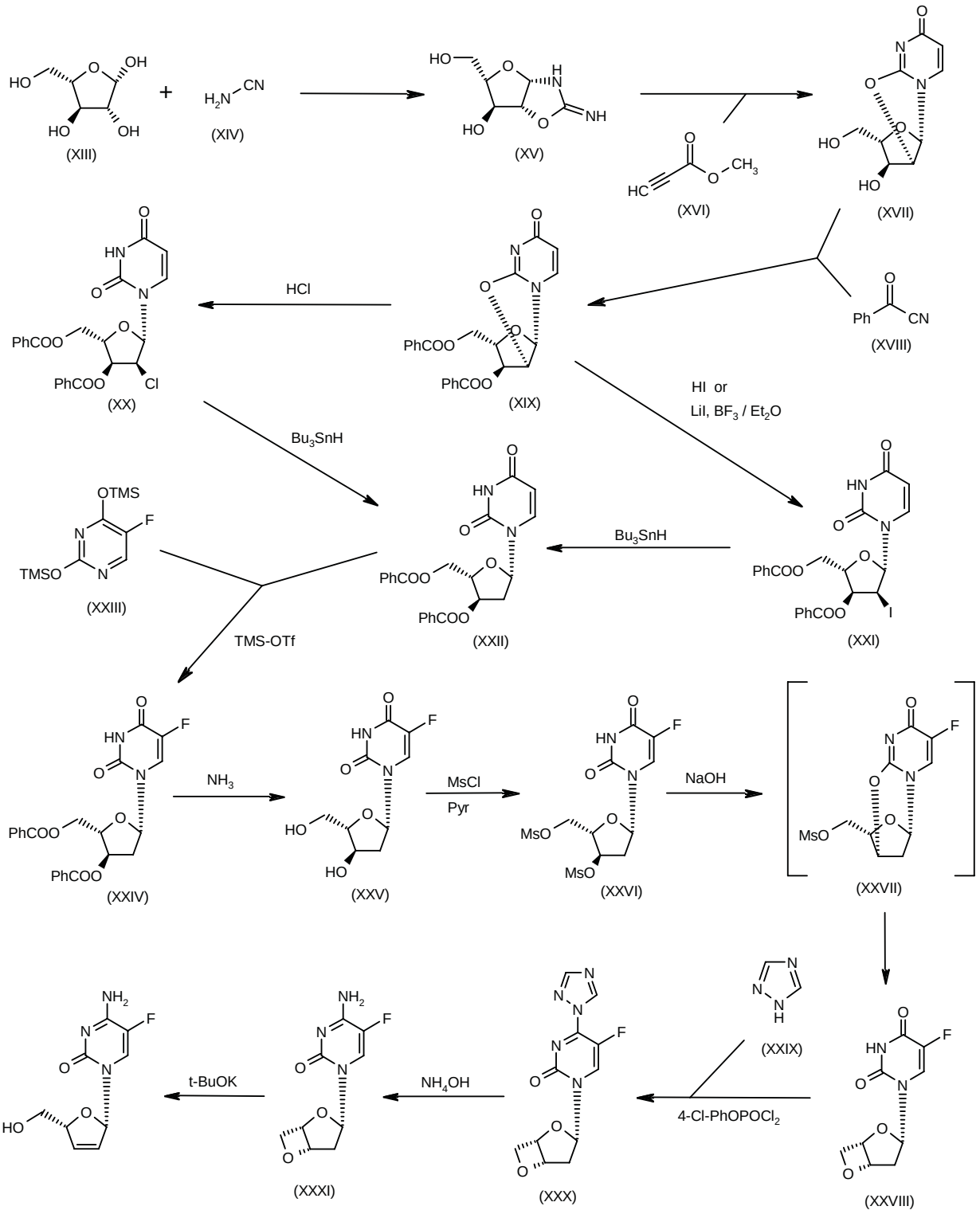
Scheme 1: Synthesis of ACH-126443



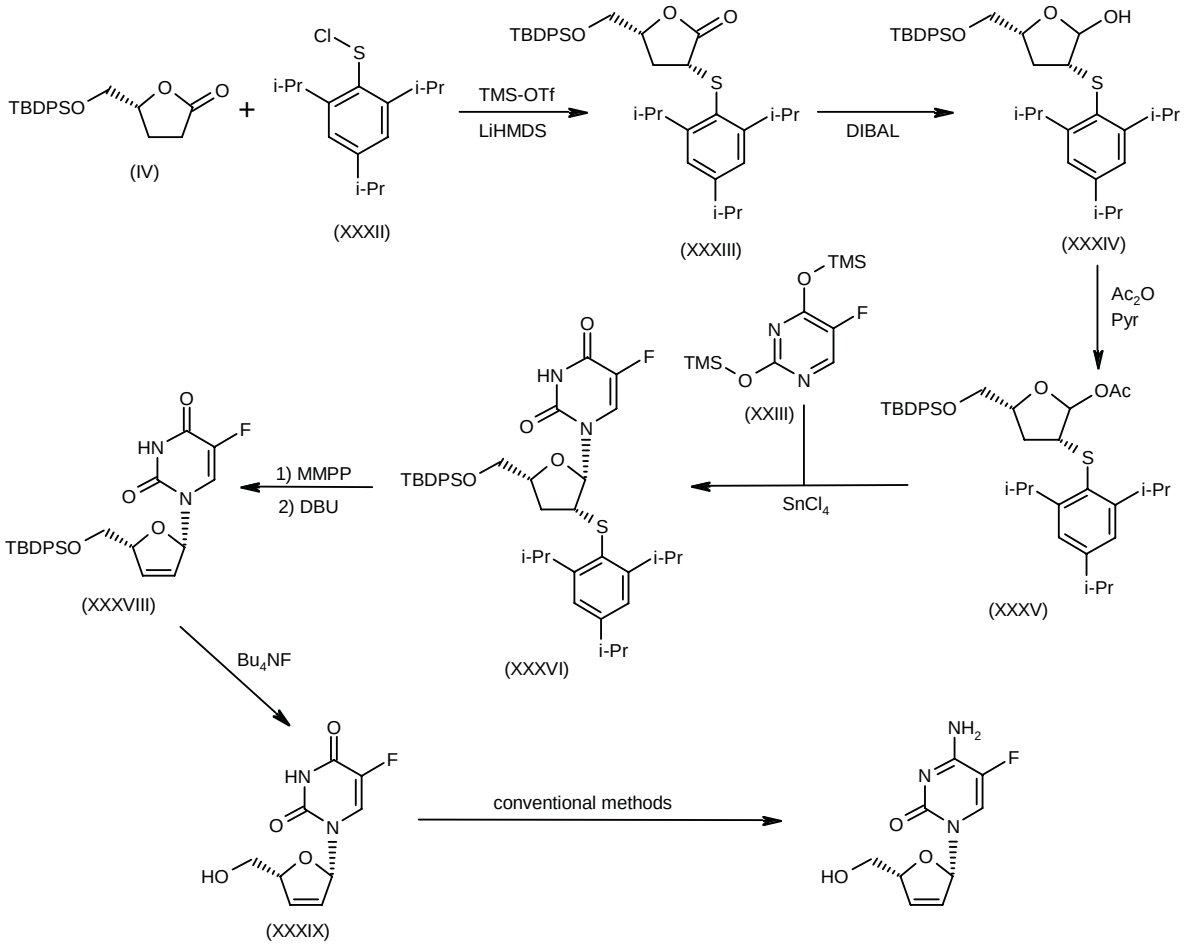
treated with MsCl and pyridine to afford the dimesylate (XXVI). Reaction of compound (XXVI) with NaOH in methanol/water provides the unstable intermediate (XXVII) that rearranges to the cyclic ether (XXVIII). Treatment of (XXVIII) with 1,2,4-triazole (XXIX) and *p*-chlorophenyl dichlorophosphate in pyridine provides the adduct (XXX), which by cleavage of the triazole ring by means of NH_4OH in dioxane gives the corresponding cytidine derivative (XXXI). Finally, this compound is treated with potassium *tert*-butoxide in DMSO (4, 5). Scheme 2.

3) Condensation of the chiral lactone (IV) with 2,4,6-tris-isopropylphenylsulfanyl chloride (XXXII) by means of LiHMDS and TMS-OTf in THF gives the adduct (XXXIII), which is reduced with DIBAL in toluene to yield the lactol (XXXIV). Reaction of compound (XXXIV) with Ac_2O and pyridine in THF affords the acetoxy derivative (XXXV), which is condensed with the silylated 5-fluorouracil (XXIII) by means of $SnCl_4$ in dichloromethane to provide the nucleoside (XXXVI). Oxidation of the sulfanyl group of (XXXVI) with magnesium monoperoxyphthalate (MMPP) in THF, followed by desulfurization by heating with DBU in refluxing toluene, gives 5'-*O*-TBDPS-2',3'-dideoxy-2',3'-didehydro-5-fluoro-β-L-uridine (XXXVII), which by treatment with Bu_4NF in THF yields 2',3'-dideoxy-2',3'-didehydro-β-L-uridine (XXXIX). Finally, this compound is converted into 2',3'-dideoxy-2',3'-didehydro-β-L-cytidine by conventional methods (6). Scheme 3.

Scheme 2: Synthesis of ACH-126443



Scheme 3: Synthesis of ACH-126443



Introduction

Human hepatitis B virus (HBV) is a partially double-stranded, circular enveloped DNA virus belonging to the Hepadnaviridae family of viruses. It replicates primarily in hepatocytes through reverse transcriptase of an RNA-replicative intermediate. HBV replication is only mildly cytopathic toward the host cell. However, the immune response to HBV-induced liver damage is the major cause of chronic hepatitis B, cirrhosis and primary liver cancer or hepatocellular carcinoma. Chronic HBV infection is the ninth leading cause of death throughout the world and the World Health Organization estimates that 1-2 million individuals die every year from hepatitis B-related disease. There are an estimated 350 million HBV carriers worldwide with nearly one-third expected to develop progressive liver disease; 1.2 million individuals in the U.S. are estimated to be HBV carriers (7).

Despite the widespread availability and use of effective vaccines, HBV infection continues to be a major global health concern. HBV is approximately 100 times more contagious than the human immunodeficiency virus (HIV-1) and is transmitted through percutaneous or permucosal exposure to infectious body fluids, sexual contact with an infected person or perinatally from an infected mother to an infant. In contrast to HIV, HBV transmission can occur in settings of constant close personal contact (*i.e.*, among family members). The clinical course and consequences of acute HBV infection are variable and depend on age; 90-95% of infected individuals recover completely. In general, the symptoms first seen in the acute phase of infection are anorexia, nausea, malaise and vomiting, followed by dark urine and jaundice. Fulminant liver failure due to the enhanced immune response to HBV is the most serious complication of acute infection but occurs in fewer than 1% of all infected individuals. Although acute HBV infection resolves in the majority of cases, a small percentage of individuals progress to chronic infection. Chronic hepatitis B infection is defined as the presence of serum hepatitis B surface antigen for at least 6 months. The risk of developing chronic infection is inversely related to age with the

highest rates observed during the perinatal period. Most individuals are asymptomatic and only those that progress to clinically apparent cirrhosis develop the symptoms of liver disease. The most common symptom of chronic HBV infection is intermittent and mild fatigue (7).

The goal of treatment of chronic HBV infection is to suppress HBV replication prior to development of irreversible liver damage. This can be accomplished with antiviral agents and immunomodulatory therapy. Over the past 10 years, research has focused on the development of direct anti-HBV agents with the ability to directly block HBV replication. This is accomplished through the inhibition of polymerase, reverse transcrriptase or other viral enzymes crucial to the viral replication process. An ideal anti-HBV chemotherapy should quickly and completely eliminate infection. However, most HBV therapies tested to date have had only limited success. Interferon-α (IFN-α) was the mainstay of hepatitis B therapy for over 2 decades. However, the response rate is poor and only a small percentage of infected individuals with active liver disease and low level viremia respond. In addition, IFN-α is administered s.c. and is associated with dose-limiting adverse events. Thus, more effective and more tolerable agents are needed or the treatment of HBV infection (7).

Naturally occurring nucleoside analogues either alone or in combination with IFN-α were used early to treat hepatitis B. However, these early agents were unsuccessful or associated with high toxicity and therefore abandoned (8-10). The search for novel nucleoside-based chemotherapies continues with agents emerging from modification of the naturally occurring nucleosides that have improved dramatically over the past 10 years. Of the new-generation nucleoside analogues, the first oral antiviral agent for the treatment of compensated chronic hepatitis B associated with HBV replication and active liver inflammation was lamivudine (3TC), originally launched in 1995 for HIV disease and later licensed for chronic HBV infection in 1998. Lamivudine is a potent and well tolerated inhibitor of HBV replication; its antiviral effects are accompanied by a reduction in serum ALT evels (a serum marker of liver inflammation) which is a predictor of e antigen seroconversion (*i.e.*, loss of viral replication). However, a major drawback of long-term (more than 12 months) lamivudine therapy is the development of drug resistance. Lamivudine-resistant HBV is characterized by amino acid site mutations in the YMDD locus of the catalytic domain of HBV polymerase. Combination therapy could prevent or delay the problem of lamivudine resistance, with agents coadministered to result in synergistic or additive effects. The development of new nucleoside analogues remains imperative. However, the goal of preventing and controlling drug resistance can result in agents that lack antiviral specificity. Thus, the search for novel anti-HBV agents continues to be a priority and extensive research is currently being carried out in this area. Viral inhibitors currently undergoing preclinical and clinical development for the treatment of hepatitis B are shown in Table I (7).

ACH-126443 (β-L-Fd4C) is an unnatural L-nucleoside reverse transcriptase inhibitor that has shown potent and selective activity against HBV. Its anti-HBV activity is 5- to 10-fold more potent than lamivudine. Because reverse transcriptase activity is also required for HIV, ACH-126443 has also shown significant efficacy against HIV (4, 11). Moreover, the agent has the potential efficacy to prevent and delay the onset of viral associated cancers. ACH-126443 was selected for further development as a treatment for chronic HBV and HIV infections.

Pharmacological Actions

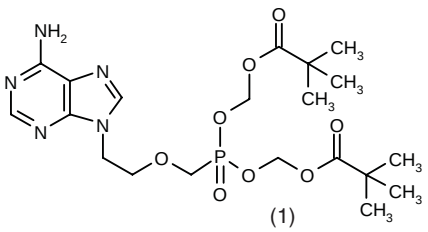
ACH-126443 was shown to be more potent than lamivudine against HBV and HIV-1 *in vitro*. In experiments using the 2215 cell line, ED_{50} values obtained for ACH-126443 were 2 nM for inhibition of both extracelluar circular and intracellular replicating HBV as compared to 17 and 30 nM, respectively, for lamivudine. Similar results were obtained in another study where the EC_{50} value for ACH-126443 against HBV was 8 nM. ACH-126443 (ED_{50} = 0.09 μM) was also more potent than lamivudine (ED_{50} = 2 μM) in inhibiting HIV-1 in MT-2 cells; another study using the MT-2/IIIb cell line also showed that ACH-126443 (EC_{50} = 0.2 μM) was 10-fold more potent than lamivudine against HIV. ED_{50} values for cytotoxicity on cell growth and mitochondrial DNA content (*i.e.*, mitochondrial DNA synthesis) after 6 days of exposure for ACH-126443 were 7 and > 100 μM, respectively, as compared to 50 and > 50 μM, respectively, for lamivudine. Further evaluation of cytotoxicity showed that ACH-126443 was not cytotoxic in terms of inhibiting cell growth in DLD-1, HepG2 (human hepatoma) Rat-1 and B16 (murine melanoma) cell lines (> 200 μM), although an IC_{50} value of 6.5 μM was obtained in one study for human T-cell lymphoblastic leukemia (CEM) cells (4, 11).

Further potent anti-HBV activity was shown for ACH-126443 that was at least 10-fold more potent than lamivudine in *in vitro* experiments using the HBV producing cell line HepG2 2.2.14. In these experiments, after 6 days of exposure to the agent, the amount of extracellular HBV DNA secreted from cells was determined. ACH-126443 was 15 times more potent than lamivudine. No effects of either agent at concentrations up to 10 μM were observed on mitochondrial DNA. The effects of ACH-126443 were reversible in experiments where HepG2 2.2.15 were treated for 6 days followed by 12 days of drug-free incubation, indicating that the presence of the agent is required to maintain inhibitory activity. The effects of lamivudine were also reversible, although the dynamics of recovery of the virus were slower for ACH-126443 (12).

The anti-HIV activity of ACH-126443 in combination with other antivirals was examined *in vitro* in MT-2 cells. Synergistic antiviral activity against HIV replication was observed for ACH-126443 in combination with D4T (stavudine) or AZT (zidovudine) while additive activity was seen when ACH-126443 was combined with ddC (zalcitibine) or ddI (didanosine). ACH-126443 had no

Table I: Viral enzyme inhibitors marketed and in development for the treatment of chronic hepatitis B (from Prous Science Integrity®).

Drug Name	Source	Status
1. Adefovir Dipivoxil	Gilead	L-2002
2. Lamivudine	GlaxoSmithKline/Shire BioChem	L-1998
3. Emtricitabine	Gilead	Phase III
4. Entecavir	Bristol-Myers Squibb	Phase III
5. Telbivudine	Idenix	Phase III
6. ACH-126443	Achillion/Vion	Phase II
7. Clevudine	Gilead	Phase II
8. Torcitabine	Idenix	Phase I/II
9. Valtorcitabine	Idenix	Phase I/II
10. Hepavir B+	Metabasis/Ribapharm	Phase I
11. LB-80317	LG Chem	Phase I
12. LB-80331	LG Chem	Phase I
13. LB-80380	LG Chem	Phase I
14. MCC-478	Lilly/Mitsubishi Pharma	Phase I
15. MIV-210+	Medivir	Phase I
16. Amdoxovir	Gilead	Preclinical
17. Bay-41-4109	Bayer	Preclinical
18. DW-977+	Dong-Wha	Preclinical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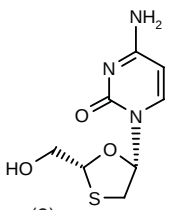
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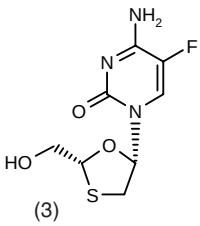
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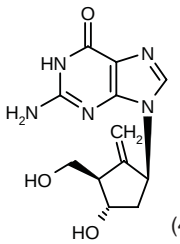
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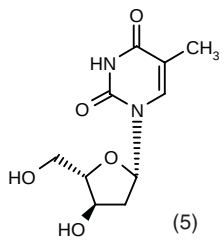
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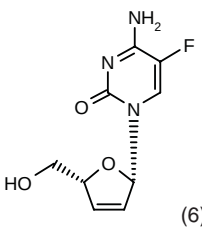
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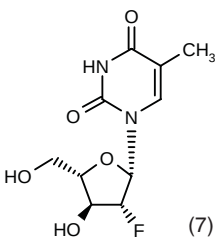
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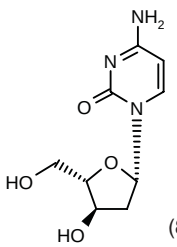
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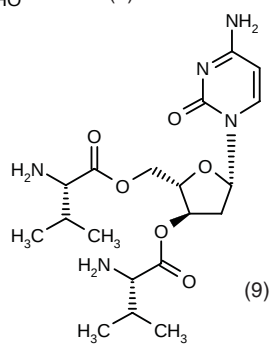
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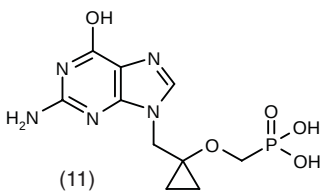
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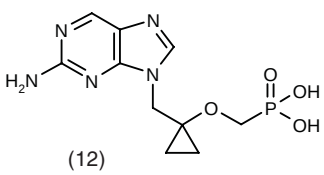
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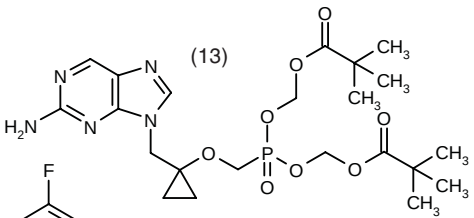
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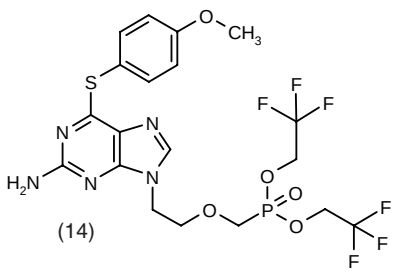
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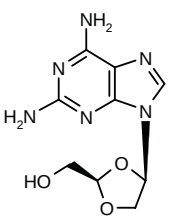
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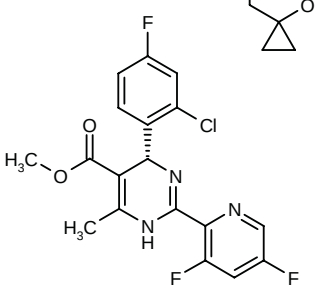
(17)

+Structure not yet detected

effects on mitochondrial DNA synthesis at concentrations up to 10 μM and the agent actually protected cells against cytotoxicity induced by D4T, ddC and ddI (13).

The sensitivity of several lamivudine-resistant HBVs (including single mutations: pL526M, pV553I and pA546V and double mutations: pL526MM550V, pM550IV5531 and pA546VM550I) to ACH-126443 was examined *in vitro* in transiently transfected HepG2 cells. Both the V553I and L526M mutants which are 3- and 6-fold resistant to lamivudine, respectively, had a reduced sensitivity to the agent as compared to wild-type; the double mutant L526MM550V which is more resistant to lamivudine also exhibited reduced sensitivity to ACH-126443. Although HBV with the single A546V mutation was sensitive to ACH-126443, resistance was apparent with the double A546VM550I mutation. Reduced sensitivity of the HBV mutants was found to be associated with a reduced susceptibility of the mutated viral DNA polymerase (14).

The sensitivity of the cell lines HepG2-WT10, HepG2-SM1 and HepG2-DM2 transfected with different HBV genomes (wild-type HBV-adr, L526M mutant and L526MM550V mutant, respectively) to ACH-126443 were examined *in vitro*. In contrast to transiently transfected cells, these cell lines stably produce lamivudine-sensitive and -resistant HBV virions. The IC_{50} values obtained for ACH-126443 versus lamivudine in the HepG2-WT10, HepG2-SM1 and HepG2-DM2 cell lines were 0.0009 ± 0.0001 *vs.* 0.005 ± 0.001 μM, 0.0027 ± 0.0003 *vs.* 0.035 ± 0.004 μM and 0.21 ± 0.03 *vs.* 8 ±1.6 μM, respectively. Results were comparable to those obtained using transiently transfected cell systems (15).

The sensitivity of wild-type HIV-1 and 65 clinical HIV-1 strains with known nucleoside (*e.g.*, M41L, M184V, T215Y and Q151M) and nonnucleoside (*e.g.*, K103N, Y181C and G190A) resistance mutations to ACH-126443 were examined *in vitro*. The IC_{50} values obtained for ACH-126443 against wild-type and all mutant strains were unchanged (0.1-0.3 μM) with the exception of the M184V mutants where the IC_{50} obtained was 1-4 μM. In contrast, the IC_{50} values for lamivudine against wild-type HIV and M184V mutants were 1-4 μM and > 30 μM, respectively (16).

The development of drug-resistant mutations was examined in an *in vitro* study using primary human peripheral blood mononuclear cells (PBMCs) from healthy donors seronegative for HIV-1 and HBV; PBMCs were experimentally infected with HIV-1LAI and stimulated with phytohemagglutinin (2-4 days). Both lamivudine and ACH-126443 selected for the V184 mutation which was first observed at week 2 and 7, respectively on passage. ACH-126443 also selected for the K/R65 mutations, suggesting a link between the 2 mutations *in vitro*. Other agents tested (*e.g.*, emtricitabine, nelfinavir, L-FddC, AZMC, novuridine, amprenavir) also selected for the V184 mutation, suggesting that these agents cannot be combined clinically to prevent emergence of resistant viruses (17).

The potent antiviral effects of ACH-126443 were demonstrated in *in vitro* and *in vivo* duck HBV infection models. In a cell-free system, the triphosphate form of ACH-126443 (β-L-Fd4C-TP) dose-dependently inhibited incorporation of dCTP into viral minus-strand DNA of duck HBV (IC_{50} = 0.2 ± 0.064 *vs.* 6.3 ± 2.2 μM for the triphosphate form of lamivudine). β-L-Fd4C-TP was found to be a competitive inhibitor of dCTP incorporation and caused premature DNA chain termination. Results from other experiments using infected primary duck hepatocyte cultures showed that ACH-126443 inhibition of viral DNA synthesis was long-lasting, although viral covalently closed circular DNA (CCC DNA) was not cleared by treatment (18).

Short-term treatment *in vivo* of experimentally infected ducks with ACH-126443 (0.2, 2, 5, 20 and 25 mg/kg/day i.p. for 5 days starting 3 days postinoculation) was more potent than lamivudine, with peak inhibitions of viremia of 97 and 87% achieved with a dose of 25 mg/kg for the respective agents. The effects of ACH-126443 on viral DNA synthesis in the liver were potent since DHBV replicative intermediates and CCC DNA were almost completely suppressed in contrast to lamivudine which induced only moderate effects. A relapse of viral replication occurred in all ACH-126443-treated animals after drug withdrawal. No liver toxicity was observed in these experiments. Long-term treatment with ACH-126443 (25 mg/kg i.p. from days 3-7 postinoculation followed by 25 mg/kg 3 times/week for 3 weeks) was also more effective than lamivudine. During the induction phase, peak inhibition of viremia was 97% for ACH-126443 as compared to 80% for lamivudine. Suppression of viremia was sustained in all ACH-126443-treated animals during the maintenance phase and marked suppression of all viral DNA replicative intermediates and CCC DNA was observed. Long-term ACH-126443 treatment also suppressed viral antigen expression within the liver and decreased intrahepatic inflammation. In contrast, viremia was not totally suppressed in lamivudine-treated animals and progressively declined to a peak viremia greater than controls at 16 days; intrahepatic synthesis of viral DNA was not decreased in lamivudine-treated animals as compared to controls. Further analysis of results after drug withdrawal after long-term treatment indicated that prolonged administration of ACH-126443 delayed the occurrence of the onset of viremia No evidence of liver toxicity was observed in any experiments (18).

The antiviral efficacy of ACH-126443 was demonstrated *in vivo* in woodchucks chronically infected with the woodchuck hepatitis virus (WHV). Short-term treatment with the agent (1 mg/kg/day i.p. for 4 and 14 days) resulted in rapid and marked reductions in serum WHV DNA levels (a 9.2-fold decrease with 15 days of treatment) and WHV endogenous polymerase activity (WHV EPA; a 47.8-fold reduction with 15 days of treatment); viremia rebounded after drug cessation. When compared to short-term treatment with lamivudine (1 mg/kg/day i.p. for 15 days), ACH-126443 was concluded to have significantly more antiviral activity; both controls and lamivudine-treated animals displayed stable or increased serum WHV DNA levels and WHV EPA levels throughout treatment (19).

Long-term treatment with ACH-126443 (4 mg/kg i.p. for 3 days followed by 4 mg/kg i.p. twice weekly for 2, 5, 9 or 15 weeks) caused significant inhibition of viremia (a 21.5-fold decrease with 5 weeks of treatment) with marked decreases in WHV EPA and serum WHV DNA seen (a 11.4-fold with 5 weeks of treatment). An increase in viremia was observed in 3 of 6 animals receiving twice weekly treatment. However, when maintenance therapy was modified at week 6 to thrice weekly for 9 more weeks, the antiviral effects were sustained in these animals until the end of treatment. Long-term ACH-126443 (4 mg/kg i.p. for 5 days followed by 4 mg/kg thrice weekly for 8 weeks) treatment was compared to lamivudine (10 mg/kg) administered in a comparable schedule. A rapid and significant reduction in viremia was observed in ACH-126443-treated animals (a 38.7-fold decrease in WHV EPA and a 31-fold decrease in WHV DNA) which was sustained until the end of treatment. In contrast, spontaneous fluctuations in viremia levels were detected in lamivudine-treated animals so that levels first dropped and the followed by a rise and another decrease. At the end of treatment, viremia returned to baseline in 4-6 and 10 weeks in ACH-126443- and lamivudine-treated animals, respectively. Although long-term ACH-126443 was associated with marked inhibition of intrahepatic viral DNA synthesis, CCC DNA persisted and may explain why infected hepatocytes were not cleared with ACH-126443 treatment. ACH-126443 treatment was associated with a reduction in inflammatory activity and an absence of ultrastructural changes in hepatic mitochondria, biliary canaliculi and bile ducts. All animals treated with ACH-126443 or lamivudine experienced weight loss and transient skin pigmentation and there was no indication that either agent could prevent the development of hepatocellular carcinoma (19).

ACH-126443 is considered to be an agent with the potential to prevent or delay the onset of viral associated cancer and preclinical research has been initiated in this area (20, 21).

Metabolism and Pharmacokinetics

Metabolism studies using cultured HepG2 cells revealed that ACH-126443 was metabolized intracellularly to mon-, di- and triphosphate forms. When compared to lamivudine at similar concentrations, there was a higher degree of phosphorylation to the triphosphate form for ACH-126443. In addition, the 5'-triphosphate form of ACH-126443 was retained within the cells longer than the 5'-triphosphate form of lamivudine. The apparent Km of the intracellular phosphorylated metabolites formed was higher for ACH-126443 than lamivudine. Cytosolic deoxycytidine kinase was found to be responsible for formation of the monophosphates (K_m = 100 μM) from ACH-126443; ACH-126443 was not recognized *in vitro* by human mitochondrial deoxypyrimidine nucleoside kinase and the agent was not a substrate for deoxycytidine deaminase. The triphosphate form of ACH-126443 was found to inhibit HBV DNA polymerase in competition with dCTP with a K_i of 0.069 ± 0.015 μM (12, 13).

A phase I single dose, randomized, ascending dose, placebo-controlled trial conducted in 48 fasted healthy volunteers examined the safety, pharmacokinetics and bioavailability of ACH-126443 (1, 5, 10, 20, 50 and 100 mg p.o. coadministered with 20 ml Extra Strength Maalox®). The agent was well tolerated at all doses and no drug-related adverse events were reported. Plasma concentrations of the agent could not be detected with the lowest 1 mg dose. However, the pharmacokinetics obtained at doses of 5 mg and higher suggested good oral bioavailability and dose-proportional absorption; AUC values increased approximately dose-proportionally from 172-1935 ng·h/ml. The mean C_{max} ranged from 15.8-421 ng/ml which was achieved at 60-90 min after dosing for all doses and the $t_{1/2}$ was about 6-8 h (22, 23) (see Table II).

Clinical Studies

The safety and efficacy of oral ACH-126443 (1, 5, 10, 20, 50 and 100 mg once daily coadministered with a commercial antacid for 14 days) was examined in a randomized, blinded, placebo-controlled, sequential dose trial involving 40 adults with chronic HBV infection (median baseline plasma HBV DNA = 7 $\log_{10}$; median baseline ALT = 78 IU/ml). The agent was well tolerated with no clear drug-related adverse events reported. Mild nausea was seen but was related to the antacid and changes in liver enzymes unrelated to dose were considered to be disease-related. While mean plasma HBV DNA did not changes after 14 days of treatment, a nonsignificant reduction of 0.5 $\log_{10}$ was seen in patients administered the 1 mg/kg dose and significant possibly dose-related reductions of 1.5-2.5 $\log_{10}$ were observed in groups administered the higher doses of the agent. At the end of therapy HBV DNA and ALT levels returned to baseline values although no flares were reported. It was concluded that the rapid antiviral effects observed with ACH-126443 was comparable or superior to other compounds in clinical use (24) (see Table II).

A phase I/II randomized, multicenter, blinded, placebo-controlled, ascending-dose trial conducted in 36 treatment naive-HBV infected subjects (mean baseline plasma HBV DNA = about 7 $\log_{10}$; mean baseline ALT = 79 IU/ml) examined the safety and efficacy of oral ACH-126443 (1, 5, 10, 20, 50 and 100 mg once daily for 14 days). The agent was well tolerated with no drug-related adverse events seen. Peak plasma levels of the agent (20 ng/ml or greater) occurred within 1 h of dosing which exceeded the IC_{50} value for wild-type HBV *in vitro* by 50-fold or greater. Moreover, the IC_{50} value for a YMDD mutant HBV was achieved with the 10 mg dose and was exceeded 2- to 20-fold with doses of 20 mg or higher. Marked and significant suppression of viral replication was seen with doses of 5-100 mg/day; a mean decline in plasma HBV DNA of 1.5-3 $\log_{10}$ was reported for these

Table II: Clinical studies of ACH-126443 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis B, chronic hepatitis		ACH-126443, 1 mg po (n=8) ACH-126443, 5 mg po (n=8) ACH-126443, 10 mg po (n=8) ACH-126443, 20 mg po (n=8) ACH-126443, 50 mg po (n=8) ACH-126443, 100 mg po (n=8) Placebo (n=16)	64	ACH-126443 was well-tolerated at single doses up to 100 mg, with no apparent dose- or drug-related adverse events	22
Hepatitis B, chronic hepatitis	Randomized, double-blind, multicenter	ACH-126443, 1 mg po od x 14 d ACH-126443, 5 mg po od x 14 d ACH-126443, 10 mg po od x 14 d ACH-126443, 20 mg po od x 14 d ACH-126443, 50 mg po od x 14 d ACH-126443, 100 mg po od x 14 d Placebo	40	ACH-126443 was well-tolerated, with no apparent dose- or drug-related adverse events, and exhibited rapid and potent anti-hepatitis B virus activity comparable or superior to that seen with other agents	24
Hepatitis B, chronic hepatitis	Randomized, double-blind, multicenter	ACH-126443, 1 mg po od x 14 d ACH-126443, 5 mg po od x 14 d ACH-126443, 10 mg po od x 14 d ACH-126443, 20 mg po od x 14 d ACH-126443, 50 mg po od x 14 d ACH-126443, 100 mg po od x 14 d Placebo	36	ACH-126443 was well-tolerated, without apparent drug-related adverse events, and showed potent antiviral activity in patients with hepatitis B infection	25

dose groups after 14 days of treatment. There was no evidence of drug accumulation in plasma although viral suppression was sustained after drug withdrawal. It was suggested that this was due to the active intracellular triphosphate metabolite of ACH-126443 which is eliminated more slowly than the parent agent (25) (see Table II).

A phase II trial is currently under way examing the efficacy and safety of ACH-126443 as a treatment for HBV-infected patients who failed lamivudine. ACH-126443 continues to undergo phase II testing as a treatment for hepatitis B and HIV-1 infection (26).

Source

Discovered at Yale University, New Haven (US); licensed to Vion Pharmaceuticals, Inc. (US), who licensed the drug to Achillion Pharmaceuticals, Inc. (US).

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