Drugs of the Future 2006, 31(12): 1035-1041

CCC: 0377-8282/2006
DOI: 10.1358/dof.2006.031.12.1057853

Apricitabine

Prop INN

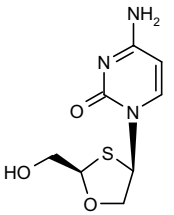
Anti-HIV Agent
Nucleoside Reverse Transcriptase Inhibitor

AVX-754
BCH-10618
(–)-BCH-10652
(–)-dOTC
SPD-754

(*R,R*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-4-yl]cytosine

(–)-2'-Deoxy-3'-oxa-4'-thiocytidine

4-Amino-1-[(2*R*,4*R*)-2-(hydroxymethyl)-1,3-dithiolan-4-yl]-2(1*H*)-pyrimidinone



$C_8H_{11}N_3O_3S$
Mol wt: 229.2574

CAS: 160707-69-7

EN: 260444

Abstract

Apricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) under development for the treatment of HIV infection. In cell-based studies, apricitabine was shown to have a low potential for mitochondrial toxicity and may therefore be associated with reduced adverse effects compared to currently available NRTIs. The agent is active against a broad range of HIV-1 strains *in vitro*, including those that are resistant to current therapies such as lamivudine. This property makes apricitabine particularly suited for use in patients who are failing first-line therapy involving these drugs. Phase I studies have demonstrated the safety of apricitabine in healthy volunteers, and a phase II study in treatment-naïve HIV-positive patients has shown that apricitabine is active against HIV-1.

Synthesis

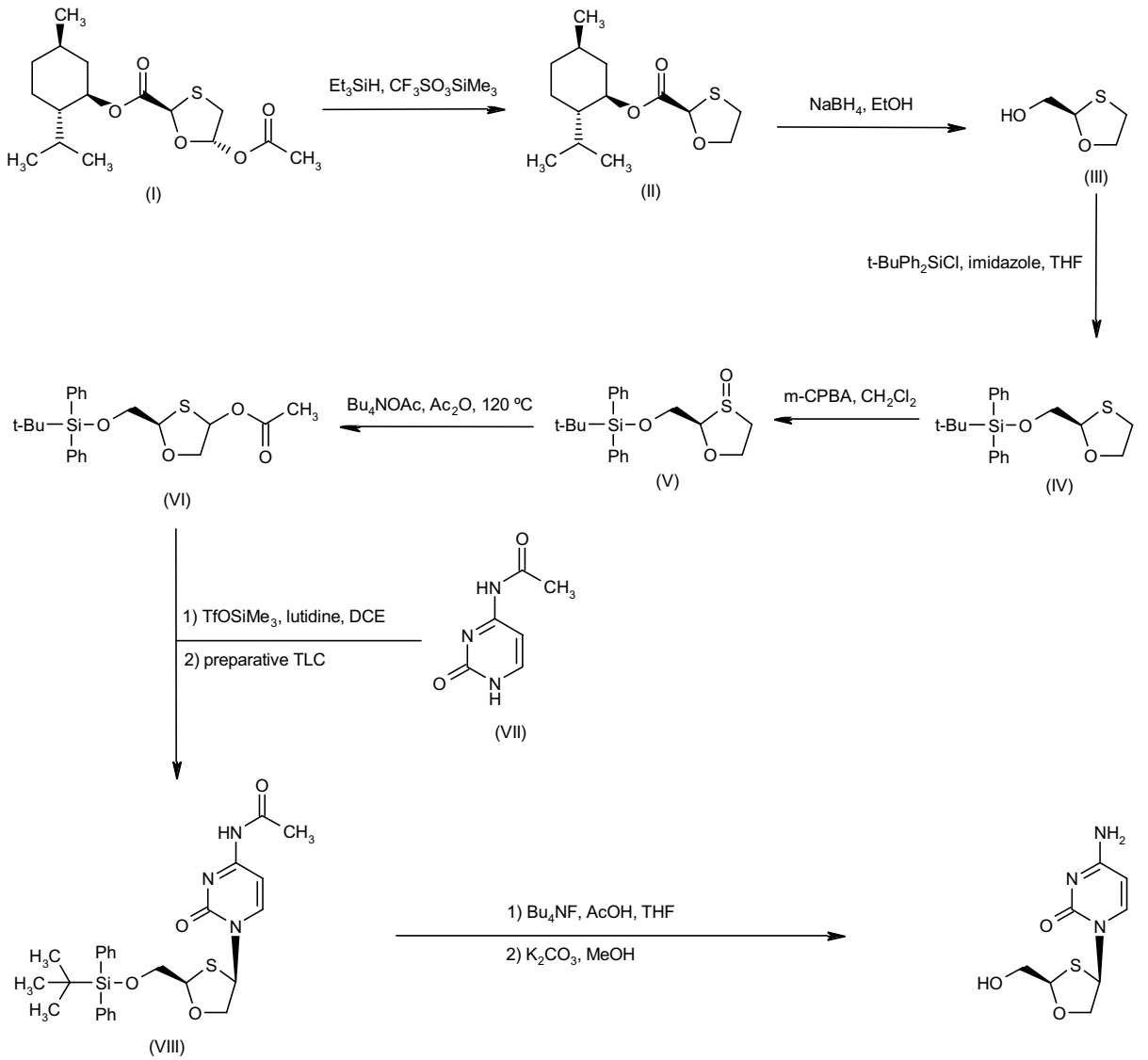
Apricitabine can be synthesized by two different methods:

1) The title compound is prepared starting from the known methyl 5(*S*)-acetoxy-1,3-oxathiolan-2(*R*)-carboxylate (I). Transposition of the 5-acetoxy group of (I) to the target 4-acetoxy derivative (VI) is achieved by the following sequence. The acetoxy group of (I) is first removed by reduction with triethylsilane to give (II), followed by ester reduction with $NaBH_4$ to give the hydroxymethyl oxathiolane (III). The primary alcohol of (III) is then protected by silylation with *tert*-butyldiphenylsilyl chloride. The resulting silylated oxathiolane (IV) is oxidized to a diastereomeric mixture of sulfoxides (V) using *m*-CPBA. Pummerer rearrangement of sulfoxides (V) in the presence of Ac_2O and Bu_4NOAc furnishes the desired 4-acetoxy thiolane (VI). Glycosylation of (VI) with *N*-acetylcytosine (VII) in the presence of trimethylsilyl triflate provides a mixture of *cis*- and *trans*-coupled products, which are separated by preparative TLC. The required *cis*-isomer (VIII) is desilylated with tetrabutylammonium fluoride, followed by acetamide hydrolysis with K_2CO_3 in MeOH, to provide the title compound (1-4). Scheme 1.

2) An asymmetric synthesis has also been reported. Oxidative cleavage of monobenzoyl glycerol (IX) by means of $NaIO_4$ provides aldehyde (X). Condensation of (X) with mercaptoethanol (XI) in the presence of polystyryl diphenylphosphane-iodine complex gives the oxathiolane (XII). Sharpless asymmetric oxidation of (XII) using *tert*-butyl hydroperoxide and L-diethyl tartrate leads to an 82:18 mixture of (*E*)- and (*Z*)-sulfoxides (XIII) and (XIV). The desired (*E*)-isomer (XIII) is then isolated by column chromatography, displaying an enantiomeric excess of 60%. Coupling of (XIII) with *N*-acetylcytosine (VII) under Pummerer rearrangement conditions leads to an equimolecular mixture of (*Z*)- and (*E*)-adducts (XV)

P. Revill, N. Serradell. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Apricitabine



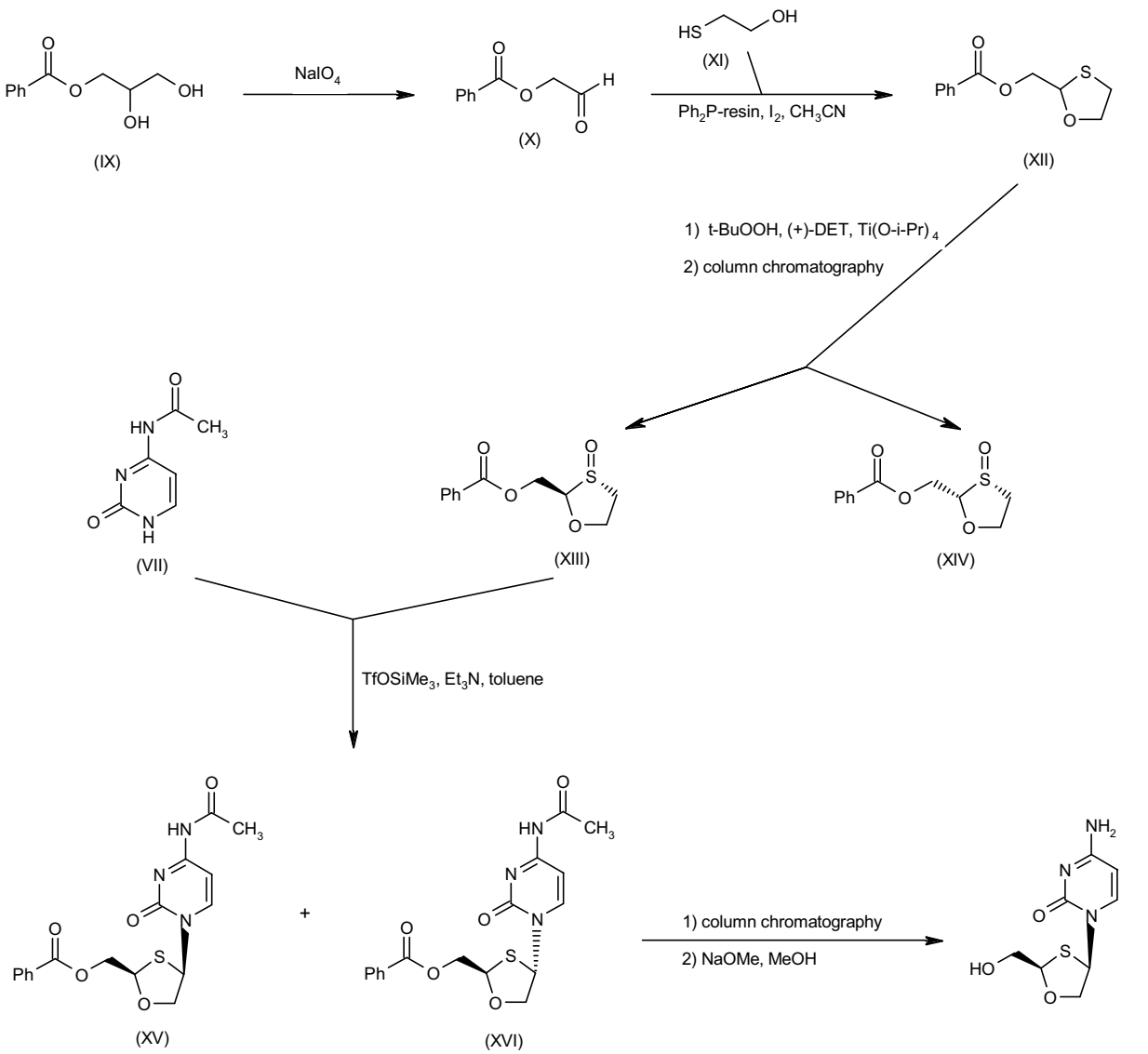
and (XVI). After chromatographic separation of the desired (*Z*)-isomer (XV), the acetyl and benzoyl protecting groups are removed by treatment with sodium methoxide (5). Scheme 2.

Background

Highly active antiretroviral therapy (HAART, a combination of 3 or more therapeutic agents, at least 2 of which are active antiretrovirals) has reduced the morbidity and mortality associated with HIV infection (6, 7). Even though HAART is effective at reducing the levels of HIV in the blood, treatment failure leading to viral rebound is still a problem. The principal reasons are poor compliance with the HAART regimen due mainly to unpleasant side effects which can lead to suboptimal therapy, and the rapid emergence of treatment-resistant strains of HIV (8-10). It is estimated that around 30% of patients develop resistance to 3 classes of antiretrovirals within 6 years of starting HAART, resulting in an increase in the risk of an AIDS-related event over that period (11).

The nucleoside reverse transcriptase inhibitors (NRTIs), including lamivudine, zidovudine, didanosine and abacavir, are a key component of HAART. With regards to drug tolerability, the adverse events associated with the long-term use of NRTIs include lipodystrophy (fat redistribution syndrome), hepatic steatosis, lactic acidosis, myopathy and peripheral neuropathy. This pattern

Scheme 2: Synthesis of Apricitabine



of symptoms resembles that caused by mitochondrial dysfunction, and NRTIs have been shown to cause mitochondrial toxicity by inhibiting human mitochondrial DNA polymerase γ, suggesting a possible causal link (12, 13).

Thus, new NRTIs with improved resistance and tolerability profiles are needed. One such compound is apricitabine (SPD-754, AVX-754, BCH-10618), a deoxycytidine analogue NRTI, which is currently in phase IIb clinical trials for the treatment of HIV infection. It is highly selective for HIV-1 reverse transcriptase and has a low potential for cellular toxicity. Cell-based studies have shown that the agent is active against HIV-1 strains resistant to current therapies, including those harboring the M184V mutation.

Preclinical Pharmacology

In enzyme assays, the K_i of apricitabine triphosphate for HIV-1 reverse transcriptase was 0.08 μM, compared to 300, 12 and 111 μM for human DNA polymerases α, β and γ, respectively. When tested against resistant HIV-1 reverse transcriptase with the M184V substitution, the IC_{50} values were only approximately twice those for wild-type enzyme (14, 15).

Experiments in human blood mononuclear cells (PBMCs) showed potent activity against wild-type and resistant HIV-1 clinical isolates, with IC_{50}/EC_{50} values ranging from 0.2 μM against wild-type isolates to 2.4 μM against lamivudine- and zidovudine-resistant isolates

bearing multiple mutations. Apricitabine was less potent in T-cell lines. It also exhibited low cellular toxicity (CC_{50} = 72-> 100 μM) and a low liability for mitochondrial toxicity (no effect at up to 200 μM in HepG2 and Molt-4 cells) or myelotoxicity (IC_{50} = 366.1 μM in human bone marrow cells). Generally additive effects were observed when it was tested in combination with other agents, including stavudine, nevirapine, didanosine, zidovudine, abacavir, lamivudine, tenofovir and saquinavir. Only low-level resistance was seen to develop slowly following multiple passages *in vitro*, with K65R, V75I or M184V mutations detected (14, 16-26).

When tested against over 200 HIV-1 clinical isolates with resistance to NRTIs, apricitabine retained significant activity against strains with multiple mutations. Sensitivity to apricitabine decreased by no more than 2-fold in the presence of up to 5 mutations at codons 41, 67, 70, 210, 215 and 219, similar to didanosine. This compares to reductions in sensitivity of > 100-fold for zidovudine, > 3-fold for lamivudine and abacavir, and > 2-fold for tenofovir. Pairwise regression analysis of fold-change values indicated that apricitabine showed significant cross-resistance with abacavir and didanosine, but less so with zidovudine and tenofovir (24, 27, 28).

Although the M184V substitution is associated with increased resistance to certain drugs such as lamivudine, it also confers potentially beneficial alterations in reverse transcriptase function that may be worth maintaining to provide improved therapeutic outcomes. Apricitabine, as well as lamivudine and abacavir, but not didanosine or zalcitabine, was shown to have the potential to select and maintain strains carrying the M184V substitution; after 10 weeks of *in vitro* culture of a wild-type HIV-1 strain in the presence of 3 μM apricitabine, 60% of viral isolates contained the M184V substitution. In a culture containing both wild-type and M184V mutant strains, 3 μM apricitabine enriched the M184V fraction and wild-type strains could not be detected (29).

Pharmacokinetics and Metabolism

In vitro studies showed that apricitabine is metabolized intracellularly to the mono-, di- and triphosphate, as well as two unidentified metabolites; the triphosphate showed an intracellular half-life of 3-4 h. In cynomolgus monkeys, oral administration of apricitabine at a dose of 500 mg/kg twice daily gave peak plasma levels of 35.5 μg/ml, well exceeding the IC_{50} value *in vitro*, reached at 1-2 h. The elimination half life was 3-5 h and there was no evidence of accumulation of apricitabine (30).

In fasted healthy volunteers (n=26) given oral doses of 400, 800 or 1600 mg, the C_{max} and AUC were linear to dose; C_{max} values were 4.1, 7.7 and 13.4 μg/ml at 1.6 h, respectively, and AUC values were 23.3, 44.9 and 80.3 μg.h/ml, respectively. Analysis of urine showed that apricitabine is principally eliminated as unchanged drug by renal excretion, with the bulk of elimination occurring within the first 8 h of administration. There was no evidence for interconversion of the (+)- and (–)-enantiomers *in vivo*. The mean half-lives for the dominant elimination phase (4-12 h) were 2.8, 3.2 and 3.7 h at doses of 400, 800 and 1600 mg, respectively. Intersubject variability was low and there was no effect of gender after adjustment for weight differences. Apricitabine was well tolerated at all doses (31-33).

In a study comparing the pharmacokinetics of apricitabine in healthy and HIV-infected subjects, single (800 mg) or multiple doses of apricitabine (600 or 800 mg twice daily for up to 8 days) were administered. The pharmacokinetics of single and multiple doses (800 mg) of apricitabine were similar in HIV^+ and HIV^- individuals; the t_{max} was 1-3 h, the $t_{1/2}$ was 3 h, the C_{max} was 7-8 μg/ml after single doses and 8-10 μg/ml after multiple doses, and the AUC_{0-24h} was 38-45 μg.h/ml irrespective of dosing regimen. Analysis of the intracellular concentration of apricitabine triphosphate after 8 days on 600 mg twice daily indicated C_{max} and C_{min} values of 3.73 and 1.45 pmol/million cells, with an intracellular $t_{1/2}$ of 6-7 h. The intracellular concentration of apricitabine triphosphate correlated well with the plasma concentration of apricitabine (34).

In an open-label, crossover study of the effects of food on the pharmacokinetics of apricitabine, 20 healthy male volunteers were randomized to a single dose of 1200 mg of apricitabine either after a high-fat breakfast or in the fasting state, with a 7-day washout period between each phase. The C_{max} values with and without food were 55 and 48.4 μg/ml, respectively, and AUC values were 8.7 and 8.1 μg.h/ml, respectively, indicating that food had no effect on the pharmacokinetics of apricitabine. Good tolerance was reported (35).

Apricitabine exhibited predictable pharmacokinetics in a clinical trial in 63 HIV^+ treatment-naïve patients (for further details see below). At doses of 200, 400, 600 and 800 mg b.i.d. p.o. for 10 days, respective C_{max} values were 2.30, 4.92, 6.62 and 9.72 μg/ml, and respective AUC_{0-12h} values were 10.1, 24.1, 29.0 and 38.1 μg.h/ml; the respective C_{max} values for 800 and 1200 mg once daily were 7.70 and 11.5 μg/ml, and the respective AUC_{0-24h} values were 35.6 and 52.9 μg.h/ml. Plasma concentrations declined with a mean $t_{1/2}$ of 2.3-3.6 h (36).

The intracellular concentration of apricitabine triphosphate was dependent on dose, with C_{max} values reaching 5.55 and 6.1 pmol/million cells at the doses of 800 mg twice daily and 1200 mg once daily, respectively. Likewise, AUC values were dose-dependent, reaching 47.9 and 68.7 h.pmol/million cells, at the respective doses; intracellular half-life was 6-7 h. A preliminary analysis indicated that the intracellular concentrations of apricitabine triphosphate are related to apricitabine plasma concentrations (37).

Safety

In a preclinical safety study in cynomolgus monkeys, no adverse effects were seen at up to 500 mg/kg/day apricitabine administered orally twice daily for 52 weeks. At the maximum tested dose (1 g/kg/day), mild and reversible mucocutaneous hyperpigmentation, gastroin-

testinal effects and changes in red blood cell counts were seen. In contrast, the racemate (BCH-10652) was associated with serious toxicity at the dose of 1 g/kg/day (38).

In a double-blind, crossover phase I study to investigate the cardiovascular safety of apricitabine, 37 healthy subjects were randomized to apricitabine at doses in excess of those currently used in clinical trials, placebo or moxifloxacin as positive control. The range of placebo-corrected Q-T intervals for subjects in the apricitabine treatment arm was –0.5 to 6.0 ms, within that considered safe. By comparison, the range for those administered moxifloxacin was 2.37 to 11.15 ms (39).

Clinical Studies

In a randomized, double-blind, dose-selection study in 63 treatment-naïve HIV-positive patients, apricitabine (200, 400, 600 or 800 mg twice daily or 800 or 1200 mg once daily) or placebo was administered for 10 days. A dose-dependent drop in viral load was seen, with reductions from baseline relative to placebo of 1.16, 1.28, 1.44 and 1.30 $\log_{10}$ copies/ml for doses of 400, 800, 1200 and 1600 mg/day, respectively, at 7 days, and reductions of 1.65 and 1.58 $\log_{10}$ copies/ml on 1200 and 1600 mg/day, respectively, at day 10. Higher doses appeared to be associated with greater viral suppression. Genotyping demonstrated that apricitabine did not select for reverse transcriptase mutations after short-term monotheraoy and that it retained activity against virus with substitutions normally associated with resistance to NRTIs. No significant changes were observed in CD4 or CD8 cell counts. All doses were well tolerated, headache being the most frequent adverse event (42% of patients on apricitabine *vs.* 30.8% of those on placebo) (36, 40-43).

Ongoing studies include a phase IIb study (AVX-201) of apricitabine compared to lamuvidine for the treatment of drug-resistant HIV (44) and a long-term phase II safety extension of this study (AVX-201E) (45).

Drug Interactions

The potential for drug interactions between apricitabine and lamivudine (both deoxycytidine analogues) was demonstrated *in vitro* in PBMCs. Although in healthy volunteers no effect was seen on plasma pharmacokinetics when the drugs were co-administered, the intracellular concentration of apricitabine triphosphate was significantly reduced by the presence of lamivudine *in vitro*, probably because of competition for intracellular deoxycytidine kinase (46, 47). Another deoxycytidine analogue, emtricitabine, likewise reduced the intracellular concentration of apricitabine triphosphate by 8-10-fold in PBMCs, although apricitabine had no effect on the intracellular concentration of emtricitabine triphosphate (48).

In the isolated perfused rat kidney, apricitabine was excreted in a nonlinear fashion at doses of 80-1600 μg; the clearance rate was greater than the glomerular filtration rate and excretion ratios and clearance decreased at high concentrations, indicating net tubular secretion of the drug by active transport pathways. Concomitant trimethoprim inhibited the excretion of apricitabine and resulted in a clearance to glomerular filtration ratio of < 1, indicating net tubular reabsorption of apricitabine in the presence of trimethoprim. These results are similar to those seen previously for lamivudine and suggested that trimethoprim may increase the exposure to apricitabine (49).

In a 2-part phase I study to identify potential interactions between apricitabine and trimethoprim, 16 healthy volunteers were administered apricitabine (800 mg twice daily) with or without a combination of trimethoprim and sulfamethazole (Septrin™; 960 mg/day). Co-administration resulted in an increase in the $AUC_{0\text{-}12h}$ and the C_{max} of apricitabine, although to a relatively small extent. This effect is consistent with observations seen in the clinic for other NRTIs, and it is anticipated that dose adjustments will not be necessary (20, 50).

Sources

Avexa Limited (AU); licensed from Shire Pharmaceuticals (GB, US).

References

1. Ashman, C., Belmonte, A.R., Cammack, N. et al. *Anti-human immunodeficiency virus and anti-hepatitis-B virus activities and toxicities of the enantiomers of 2'-deoxy-3'-oxa-4'-thiocytidine and their 5-fluoro analogues in vitro*. J Med Chem 1995, 38(1): 1.

2. Mansour, T.S. et al. *Structure-activity relationships among a new class of antiviral heterosubstituted 2',3'-dideoxynucleoside analogs*. Nucleosides Nucleotides 1995, 14(3-5): 627.

3. Wang, W. et al. *Synthesis of optically active 2',3'-dideoxy-3'-oxa-4'-thioribonucleoside analogs by transposition of a leaving group on chiral oxathiolanes via a reductive-oxidative process*. Tetrahedron Lett 1994, 35(27): 4739.

4. Jin, H., Mansour, T.S. (Shire BioChem Inc.). Subst. *1,3-oxathiolanes with antiviral properties*. EP 0756595, EP 1153924, EP 1473294, JP 1997512526, WO 1995029176.

5. Caputo, R. et al. *A new strategy for the asymmetric synthesis of 1,3-oxathiolane-based nucleoside analogues*. Eur J Org Chem 1999, (6): 1455.

6. Murphy, E.L., Collier, A.C., Kalish, L.A. et al. *Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease*. Ann Intern Med 2001, 135(1): 17-26.

7. Palella, F.J., Delaney, K.M., Moorman, A.C. et al. *Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection*. New Engl J Med 1998, 338(13): 853-60.

8. Ammassari, A., Murri, R., Pezzotti, P. et al. *Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection*. J Acquir Immune Defic Syndr 2001, 28(5): 445-9.

9. Hubbard, M. *Dealing with the obstacles in adhering to highly active antiretroviral therapy*. J Assoc Nurses AIDS Care 2006, 17(1): 18-25.

10. Struble, K., Murray, J., Cheng, B., Gegeny, T., Miller, V., Gulick, R. *Antiretroviral therapies for treatment-experienced*

patients: Current status and research challenges. AIDS 2005, 19(8): 747-56.

11. Mocroft, A., Ledergerber, B., Viard, J.P. et al. *Time to virological failure of 3 classes of antiretrovirals after initiation of highly active antiretroviral therapy: Results from the EuroSIDA study group*. J Infect Dis 2004, 190(11): 1947-56.

12. Wainberg, M.A., Sawyer, J.P., Montaner, J.S., Murphy, R.L., Kuritzkes, D.R., Raffi, F. *Challenges for the clinical development of new nucleoside reverse transcriptase inhibitors for HIV infection*. Antivir Ther 2005, 10(1): 13-28.

13. Kakuda, T.N. *Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity*. Clin Ther 2000, 22(6): 685-708.

14. de Muys, J.M., Gourdeau, H., Nguyen-Ba, N. et al. *Anti-human immunodeficiency virus type 1 activity, intracellular metabolism, and pharmacokinetic evaluation of 2'-deoxy-3'-oxa-4'-thiocytidine*. Antimicrob Agents Chemother 1999, 43(8): 1835-44.

15. Mansour, T., Wainberg, M.A., Salomon, H. et al. *Resistance profile, selectivity and cellular uptake studies of BCH-10618, BCH-10619 and BCH-10652*. Antivir Res 1998, 37(3): Abst 78.

16. Gu, Z., Ren, C., de Muys, J.M. et al. *BCH-10618, a novel nucleoside analogue with promising activity against resistant strains HIV-1*. 1st IAS Conf HIV Pathog Treat (July 8-11, Buenos Aires) 2001, Abst 244.

17. Mansour, T., Wainberg, M.A., Salomon, H. et al. *In vitro selectivity of BCH-10618, BCH-10619 and BCH-10652 against human immunodeficiency virus*. 5th Conf Retroviruses Opportunistic Infect (CROI) (Feb 1-5, Chicago) 1998, Abst 628.

18. Taylor, D.L., Ahmed, P.S., Tyms, A.S. et al. *Drug resistance and drug combination features of the human immunodeficiency virus inhibitor, BCH-10652 [(±)-2'-deoxy-3'-oxa-4'-thiocytidine, dOTC]*. Antivir Chem Chemother 2000, 11(4): 291-301.

19. Gu, Z., Allard, B., de Muys, J.M. et al. *In vitro antiretroviral activity and in vitro toxicity profile of SPD754, a new deoxycytidine nucleoside reverse transcriptase inhibitor for treatment of human immunodeficiency virus infection*. Antimicrob Agents Chemother 2006, 50(2): 625-31.

20. Cox, S. *Development of apricitabine*. 14th Int Symp HIV Emerg Infect Dis (ISHEID) (June 21-23, Toulon) 2006, Abst OP4.2.

21. Gu, Z., Nguyen-Ba, N., Ren, C. et al. *BCH-10618, a new heterosubstituted nucleoside analogue against HIV-1 infection*. Antivir Ther 2001, 6(Suppl. 1): Abst 11.

22. Richard, N., Quan, Y., Salomon, H. et al. *Selection and characterization of HIV-1 variants resistant to the (+) and (-) enantiomers of 2'-deoxy-3'-oxa-4'-thiocytidine (dOTC)*. Antivir Ther 1999, 4(3): 171-7.

23. Gu, Z., Nguyen-Ba, N., Ren, C. et al. *BCH-10618, a new potent anti-HIV-1 NRTI*. Antivir Res 2001, 51(1, Special issue): Abst 015.

24. Bethell, R.C., Collins, P., Holdich, T., Sawyer, J.P. *In vitro and in vivo antiviral activity of SPD754 against wild-type and NRTI-resistant viruses*. 15th Int AIDS Conf (July 11-16, Bangkok) 2004, Abst WePeA5642.

25. Gu, Z., Nguyen-Ba, N., Mellors, J.W., Fortier, C., Wainberg, M.A. *In vitro selection and characterisation of HIV-1 resistance to BCH-10618*. 8th Conf Retroviruses Opportunistic Infect (CROI) (Feb 4-8, Chicago) 2001, Abst 472.

26. Bethell, R.C., De Rooj, E.R., Smolders, K.G.M., Van Schijndel, H.B., Timmermans, E.C., De Baar, M.P. *Comparison of the in vitro mitochondrial toxicity of SPD754 in HepG2 cells with nine other nucleoside reverse transcriptase inhibitors*. 44th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Oct 30-Nov 2, Washington, D.C.) 2004, Abst H-207.

27. Bethell, R.C., Parkin, N.T., Lie, Y.S. *Antiviral activity of SPD754 against clinical isolates of HIV-1 resistant to other nucleoside reverse transcriptase inhibitors*. Antivir Ther 2003, 8(3): Abst 3.

28. Bethell, R.C., Lie, Y.S., Parkin, N.T. *In vitro activity of SPD754, a new deoxycytidine nucleoside reverse transcriptase inhibitor (NRTI), against 215 HIV-1 isolates resistant to other NRTIs*. Antivir Chem Chemother 2005, 16(5): 295-302.

29. Petrella, M., Oliveira, M., Moisi, D., Detorio, M., Brenner, B.G., Wainberg, M.A. *Differential maintenance of the M184V substitution in the reverse transcriptase of human immunodeficiency virus type 1 by various nucleoside antiretroviral agents in tissue culture*. Antimicrob Agents Chemother 2004, 48(11): 4189-94.

30. Bethell, R.C., de Muys, J.M., Gu, Z. et al. *The intracellular metabolism and animal pharmacokinetics of BCH-10618, a novel nucleoside analogue active against drug-resistant strains of HIV-1*. 41st Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 22-25, Chicago) 2001, Abst F-1676.

31. Francis, R.J., Lancois, L., Shiveley, L., Sawyer, J.P. *Pharmacokinetics (PK) of SPD754, a new cytidine analogue in healthy volunteers*. Antivir Ther 2003, 8(1): Abst 528.

32. Holdich, T., Shiveley, L., Sawyer, J.P. *Pharmacokinetics of single oral doses of apricitabine, a novel deoxycytidine analogue reverse transcriptase inhibitor, in healthy volunteers*. Clin Drug Invest 2006, 26(5): 279-86.

33. Forrest, A., Smith, P.F., Sawyer, J.P., Fox, L., Shiveley, L. *Single dose pharmacokinetics (PK) of SPD 754 in healthy adult volunteers*. 42nd Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 27-30, San Diego) 2002, Abst A-1406.

34. Sawyer, J.P., Struthers, S.C. *Pharmacokinetics of apricitabine in healthy volunteers and HIV-infected individuals*. 16th Int AIDS Conf (Aug 13-18, Toronto) 2006, Abst TUPE0077.

35. Holdich, T., Dennis, K. *Investigation of the influence of food upon the pharmacokinetics of SPD754*. 9th Eur AIDS Conf (Oct 25-29, Warsaw) 2003, Abst 4.1/6.

36. Cassetti, I., Cahn, P., Adams, J. et al. *Slope of viral load decline and steady state pharmacokinetics of SPD754 monotherapy administered once or twice daily in the treatment-naïve HIV+ individuals*. 9th Eur AIDS Conf (Oct 25-29, Warsaw) 2003, Abst F11/4.

37. Adams, J., Sawyer, J.P., Shiveley, L. *Intracellular SPD754 triphosphate pharmacokinetics following administration of SPD754 capsules*. 11th Conf Retroviruses Opportunistic Infect (CROI) (Feb 8-11, San Francisco) 2004, Abst 599.

38. Locas, C., Ching, S., Damment, S. *Safety profile of SPD754 in cynomolgus monkeys treated for 52 weeks*. 11th Conf Retroviruses Opportunistic Infect (CROI) (Feb 8-11, San Francisco) 2004, Abst 527.

39. *Avexa gets 'all clear' from phase I cardiac safety trial*. Avexa Press Release November 22, 2006.

40. Cahn, P., Van Leeuwen, R., Sawyer, J., Shiveley, L. *Tolerability and anti HIV-1 activity of SPD754 in 10 days monotherapy in treatment naïve patients*. 43rd Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 14-17, Chicago) 2003, Abst H-869.

41. Cahn, P., Cassetti, I., Wood, R. et al. *Efficacy and tolerability of 10-day monotherapy with apricitabine in antiretroviral-naïve, HIV-infected patients*. AIDS 2006, 20(9): 1261-8.

42. Collins, P., Shiveley, L., Anderson, C., Bethell, R.C. *Analysis of the genotypes of viruses isolated from patients after 10 days monotherapy with SPD754*. 11th Conf Retroviruses Opportunistic Infect (CROI) (Feb 8-11, San Francisco) 2004, Abst 526.

43. Bethell, R.C., Collins, P. *Genotypic and phenotypic analysis of HIV-1 isolates from patients after 10 days monotherapy with SPD754*. 44th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Oct 30-Nov 2, Washington, D.C.) 2004, Abst H-206.

44. *AVX754 (a new nucleoside reverse transcriptase inhibitor [NRTI]) to treat drug-resistant HIV (NCT00126880)*. ClinicalTrials.gov Web site 2006.

45. *A long term, safety study of apricitabine in HIV-infected subjects (NCT00367952)*. ClinicalTrials.gov Web site 2006.

46. Bethell, R.C., Adams, J., de Muys, J.M. et al. *Pharmacological evaluation of a dual deoxycytidine analogue combination: 3TC and SPD754*. 11th Conf Retroviruses Opportunistic Infect (CROI) (Feb 8-11, San Francisco) 2004, Abst 138.

47. Holdich, T., Shiveley, L., Sawyer, J. *A phase I study investigating the plasma and intracellular pharmacokinetics of SPD754 and 3TC when administered alone and in combination*. 15th Int AIDS Conf (July 11-16, Bangkok) 2004, Abst TuPeB4625.

48. Bethell, R.C., Collins, P., de Muys, J.M. et al. *An in vitro evaluation of the intracellular anabolism of SPD754 and FTC alone and in combination*. 15th Int AIDS Conf (July 11-16, Bangkok) 2004, Abst TuPeB4622.

49. Nakatani-Freshwater, T., Babayeva, M., Dontabhaktuni, A., Taft, D.R. *Effects of trimethoprim on the clearance of apricitabine, a deoxycytidine analog reverse transcriptase inhibitor, and lamivudine in the isolated perfused rat kidney*. J Pharmacol Exp Ther 2006, 319(2): 941-7.

50. Sawyer, J., Shiveley, L., Franklin, R. *Pharmacokinetics of AVX754 in combination with trimethoprim/sulphamethoxazole*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington, D.C.) 2005, Abst A-1201.