Pergamon

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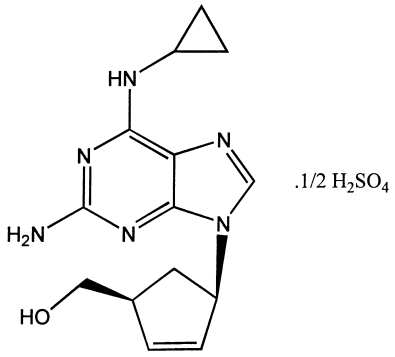
BIOORGANIC & MEDICINAL CHEMISTRY

NEW DRUGS—REPORTS OF NEW DRUGS RECENTLY APPROVED BY THE FDA

Abacavir Sulfate



C14H18N6O. ½ H_2SO_4
Mol wt: 335.366

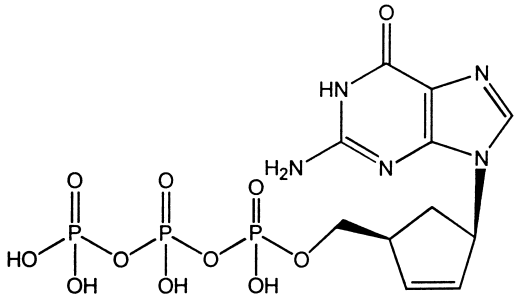
(1*S*,4*R*)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (2:1)

[CAS 188062-50-2]

ZIAGEN™, GW1592, BW159U89, BW1592, 1592U89

Therapeutic category: Anti-HIV; antiviral agent.

Mechanism of action: Abacavir is a carbocyclic nucleoside analogue with inhibitory activity against HIV. Initially, abacavir is phosphorylated intracellularly to its corresponding monophosphate. Cytosolic enzymes convert abacavir monophosphate to carbovir monophosphate (CBV-MP), which is finally phosphorylated to the biologically active moiety, carbovir triphosphate (CBV-TP). CBV-TP inhibits HIV reverse transcriptase by competing with the endogenous substrate dGTP and by chain termination subsequent to incorporation into the growing polynucleotide strand.

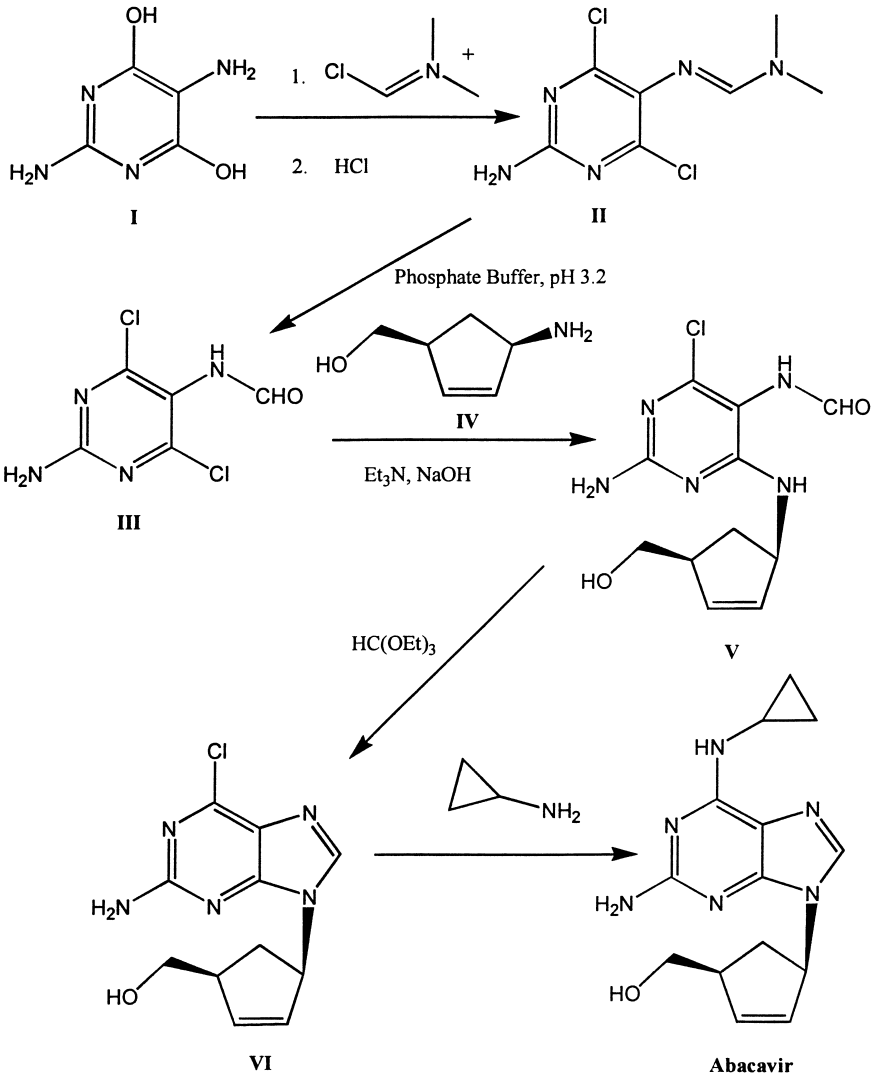


CBV-TP

Synthesis: Treatment of 2,5-diamino-4,6-dihydroxypyrimidine (**I**) with (chloromethylene)-dimethylammonium chloride yielded the dichloropyrimidine with both amino groups derivatized as amidines. Partial hydrolysis with aqueous HCl in hot ethanol gave **II**. Subseqent buffered hydrolysis at pH 3.2 yielded the formamide **III**. Condensation of

PII: S0968-0896(99)00242-4

chloropyrimidine **III** with (1*S*,4*R*)-4-amino-2-cyclopentene-1-methanol (**IV**) in the presence of triethylamine and NaOH gave **V**. The correct enantiomer (**IV**) of racemic aminocyclopentene was obtained by resolution of diastereomeric salts with D-dibenzoyltartaric acid. Cyclization of **V** to the corresponding purine was accomplished with refluxing triethyl orthoformate or diethoxymethyl acetate to give nucleoside analogue **VI**. Displacement of chloride in the purine nucleus with cyclopropyl amine in refluxing butanol afforded abacavir (Scheme 1).



Scheme 1.

Summary: Abacavir exhibits antiviral activity against clinical isolates of HIV in cell culture with a potency similar to that of zidovudine (AZT). HIV isolates with reduced sensitivity to abacavir have been isolated from patients and in vitro. Mutations in RT include K65R, L74V, Y115F, and M184V, with M184V and L74V being the most commonly detected substitutions in clinical isolates. Little cross resistance was seen in vitro between abacavir and zidovudine or stavudine; however, M184V is a substitution associated with resistance to lamivudine (3TC). The response to abacavir was reduced or eliminated in patients with isolates resistant to multiple nucleoside analogues. Abacavir is rapidly and extensively absorbed after oral dosing in humans with excellent bioavailability (83%). Significant CNS penetration occurs in patients. Abacavir has been approved for treatment of HIV infection in combination with other anti-HIV agents. In a study of patients receiving abacavir (300 mg b.i.d.), lamivudine (150 mg b.i.d.), and zidovudine (300 mg b.i.d.), approximately 70% of patients had less than 400 copies/mL of HIV RNA at 16 weeks. Significant reduction in viral load has also been seen with abacavir plus protease inhibitor combinations. The antiviral effect of abacavir in combination with other antiviral agents was maintained for at least 48 weeks in one study. Abacavir is generally well tolerated with nausea, diarrhea, headache and rash being some of the most common adverse effects. In ongoing clinical studies, approximately 5% of patients receiving abacavir developed a hypersensitiviy reaction. This reaction

usually resolved upon discontinuation of abacavir; however, resumption of abacavir treatment in these patients has resulted in extremely severe reactions, including fatalities.

Manufacturer: Glaxo Wellcome

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