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Bevirimat

Prop INN

Anti-HIV Agent
Viral Maturation Inhibitor

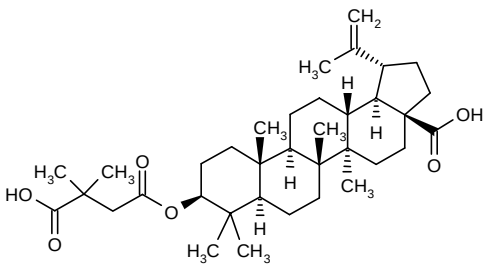
Bevirimat Dimeglumine (USAN)
PA-457
YK-FH312

[1S-(1α,3aβ,5aα,5bβ,7aα,9β,11aβ,11bα,13aβ,13bα)]-1-Isopropenyl-9-(3,3-dimethylsuccinyloxy)-5a,5b,8,8,11a-pentamethylperhydrocyclopenta[*a*]chrysene-3a-carboxylic acid

3β-(3-Carboxy-3-methylbutyryloxy)lup-20(29)-en-28-oic acid

O-(3,3-Dimethylsuccinyl)betulinic acid

InChI=1/C36H56O6/c1-21(2)22-12-17-36(30(40)41)19-18-34(8)23(28(22)36)10-11-25-33(7)15-14-26(42-27(37)20-31(3,4)29(38)39)32(5,6)24(33)13-16-35(25,34)9/h22-26,28H,1,10-20H2,2-9H3,(H,38,39)(H,40,41)/t22-,23+,24-,25+,26-,28+,33-,34+,35+,36-/m0/s1



$C_{36}H_{56}O_6$
Mol wt: 584.8262

CAS: 174022-42-5

EN: 246885

Abstract

Despite the advances made in the treatment of HIV/AIDS, particularly with the widespread use of highly active antiretroviral therapy (HAART), side effects and the emergence of resistant strains of virus remain major problems. Therefore, a major focus of antiretroviral research is the discovery of compounds with novel structures and/or mechanism(s) of action. Bevirimat is a first-in-class maturation inhibitor derived from betulinic acid which was shown to have potent and selective activity against HIV-1, including resistant strains. Further studies revealed that its mechanism of action involves disruption of a late step in Gag processing. Clinical studies indicated good efficacy and safety after once-daily doses and phase II trials are under way.

Synthesis

Bevirimat can be synthesized from betulinic acid as follows:

Betulinic acid (I) is extracted from the leaves of *Syzigium claviflorum* (1). Acylation of (I) with 2,2-dimethylsuccinic anhydride (II) in the presence of DMAP in refluxing pyridine furnishes the target 3',3'-dimethylsuccinyl betulinic acid along with minor amounts of the undesired 2',2'-dimethyl regioisomer (III), which is separated by means of preparative HPLC (2-5). Scheme 1.

Introduction

According to UNAIDS (2006 Report on the Global AIDS Epidemic [UNAIDS]), there are currently about 40 million adults and children living with HIV/AIDS worldwide, and the cumulative death toll over the first 25 years of the HIV pandemic was in excess of 25 million, as reported at the XVI International AIDS Conference in 2006.

A growing number of antiretroviral agents and combinations are available for the treatment of HIV/AIDS. The current standard of care is highly active antiretroviral therapy, or HAART, a combination of 3 or more therapeutic agents, at least 2 of which are active antiretrovirals. The use of HAART has significantly reduced the morbidity and mortality associated with HIV infection (6, 7). However, although HAART is effective at reducing the levels of HIV in the blood, treatment failure leading to viral rebound remains a problem. The main reasons are poor compli-

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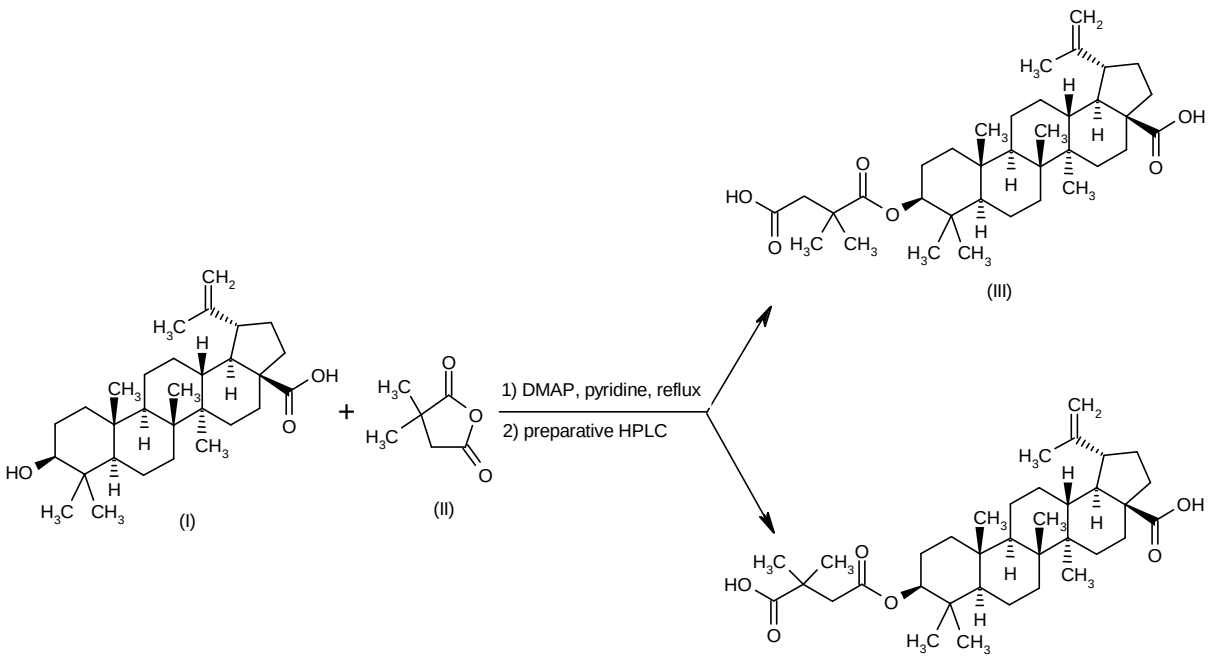
Scheme 1: Synthesis of Bevirimat



ance with the HAART regimen due in large part to unpleasant side effects which can lead to suboptimal therapy, and the rapid emergence of treatment-resistant strains of HIV (8-11). Moreover, it has been estimated that up to 10% of HIV-infected individuals are resistant to all classes of reverse transcriptase and protease inhibitors (12), and the main focus of current antiretroviral research is therefore the discovery of new compounds with novel structures or mechanism(s) of action. Promising agents under development include attachment inhibitors, CCR5 co-receptor antagonists, CXCR4 co-receptor antagonists and integrase inhibitors (10, 13, 14).

The natural compound betulinic acid, isolated from *S. claviflorum*, was found to possess anti-HIV activity and chemical modifications were undertaken in an attempt to identify potent anti-HIV agents, leading to the discovery of bevirimat (PA-457, YK-FH-312) as a compound with a novel mechanism of action (1, 2). Further studies demonstrated bevirimat to be a first-in-class maturation inhibitor with potent activity against HIV-1 that acts by disrupting Gag processing (15-24). Bevirimat, which was granted fast track designation by the FDA in 2004, is presently in phase II clinical evaluation (25).

Preclinical Pharmacology

The activity of bevirimat in inhibiting HIV replication was studied both *in vitro* and *in vivo*. With a mean IC_{50} of 10.3 nM against wild-type isolates in peripheral blood mononuclear cells (PBMCs), bevirimat demonstrated antiviral activity comparable to the approved drugs zidovudine and indinavir (IC_{50} = 4.3 and 8.8 nM, respectively), while being significantly more active than the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (IC_{50} = 40.0 nM). When tested against a range of resistant isolates using MT-2 cells, bevirimat retained low nanomolar inhibitory activity, in contrast to approved drugs. Its activity was also found to be specific for HIV-1, with no effect against HIV-2 or SIV. The therapeutic index for bevirimat was reported to be > 2,500 (CC_{50} = 25 μM). When combined with approved anti-HIV drugs, bevirimat exhibited synergy or additive activity (16, 17, 26, 27). *In vivo* studies were carried out in NL4-3-infected SCID-hu Thy/Liv mice over a 21-day period. Oral administration of a salt of bevirimat reduced viral load in a dose-dependent manner, causing reductions of 2.1, 0.9 and 0.3 $\log_{10}$ copies/ml, respectively, at doses of 100, 30 and 10 mg/kg/day (26).

The antiviral mechanisms of bevirimat were extensively studied. Bevirimat was found not to act by blocking virus attachment or entry or by inhibiting reverse transcriptase, integrase or protease (2, 17, 27). Preliminary experiments using a MAGI (multinuclear-activation galactosidase indicator) assay indicated that bevirimat interferes with viral maturation by disrupting a late step in Gag processing, specifically inhibiting the conversion of the capsid (CA) precursor p25 to the mature CA protein p24, resulting in the release of noninfective viral particles (17-19). Further studies indicated that bevirimat specifically protects the CA-p2 (or CA-SP1) cleavage site from processing by the viral protease during virion maturation, a novel anti-HIV mechanism. This was confirmed in viral resistance studies with the drug (20-24, 28-30).

In vitro, 5 amino acid changes (H226Y, L231M, L231F, A1V and A3V) conferring bevirimat resistance were identified; all were located at the CA-SP1 junction. However, resistance to bevirimat was not detected *in vivo* during a single-dose phase I/II and a 10-day multiple-dose phase II study in patients (28, 31). Also, in some cases, resistant mutants showed reduced viral fitness (20, 28, 29), and resistant viruses remained susceptible to all other classes of anti-HIV drugs (29, 30).

Pharmacokinetics and Metabolism

Preclinical studies carried out in rats demonstrated that orally administered bevirimat was metabolized to several glucuronide conjugates, including a di-glucuronide and two mono-glucuronides, which were mainly eliminated in bile. Cumulative biliary excretion demonstrated excretion mainly in the form of a mono-glucuronide. The metabolites displayed relatively high stability *in vitro* (32).

To characterize the metabolic profile of bevirimat, the compound was tested in a variety of *in vitro* systems, and the drug was administered orally and intravenously to mice, rats, marmosets and dogs to characterize its *in vivo* disposition. Results of *in vitro* studies indicated that only rat liver microsomes significantly metabolized bevirimat. No significant inhibition of cytochrome P-450 CYP1A2, CYP2C19, CYP2D6 or CYP3A4 was seen at concentrations up to 100 μM, while CYP2C9 was inhibited with an IC_{50} of about 10 μM; no inhibition of human P-glycoprotein was observed (33, 34). The oral bioavailability of bevirimat was greatest in marmosets (about 60%) and lowest in dogs (about 10%), and the half-life was also longest in marmosets (about 14 h); bioavailability in rats was 14% and the terminal half-life was about 2 h (27, 34).

The oral bioavailability and the main elimination routes of bevirimat were evaluated *in vivo* in rats administered the drug i.v. (5 mg/kg) or orally (25 mg/kg as the disodium salt); rats with chronic biliary catheters were also studied. After i.v. administration, bevirimat showed moderate systemic clearance of 0.45 ± 0.128 l/h/kg, an estimated terminal $t_{1/2}$ of 1.4 h and a volume of distribution of 0.78 l/kg; after oral administration, the mean C_{max} was 3.6 mg/ml and the bioavailability was 21 ± 12%. Neither bevirimat nor glucuronide was detected in urine. Although negligible amounts of unchanged drug were detected in bile, a significant amount of the dose was recovered as bevirimat after treatment of bile with β-glucuronidase. Bile collection reduced the i.v. AUC of bevirimat from 11.8 to 7.14 mg.h/ml, indicating that a significant portion of the dose may be subject to enterohepatic recycling. The results indicate that the clearance of bevirimat in rats occurs primarily via glucuronidation with subsequent biliary excretion (35).

The pharmacokinetics of bevirimat were also evaluated in clinical studies. A double-blind, placebo-controlled, dose-escalation study of single doses of bevirimat (25, 50, 100 and 250 mg) was carried out in 32 healthy male volunteers. Bevirimat was rapidly absorbed, with very high plasma levels (2.3-31.1 μg/ml) and a long half-life (2.5 h at 250 mg). The results suggested that therapeutic concentrations (about 2.3 μg/ml) can be achieved with a single daily oral dose as low as 50 mg. The drug was well tolerated (36).

Another double-blind, placebo-controlled, dose-escalation study assessed the pharmacokinetics of multiple oral doses (25, 50 and 100 mg once daily for 10 days) in 24 healthy male volunteers. Bevirimat was rapidly absorbed, achieving very high plasma levels (C_{max} = 2.62, 6.02 and 11.09 μg/ml, respectively, on day 1, and 7.98, 15.58 and 31.58 μg/ml, respectively, on day 10) and showing a long half-life (56.3-68.9 h). Both peak plasma levels and exposure were dose-dependent, and 3-5-fold plasma accumulation was seen with multiple dosing. Target therapeutic concentrations could be safely achieved even at the lowest dose (37).

Single oral doses (75, 150 and 250 mg) of bevirimat were evaluated for pharmacokinetics/pharmacodynamics (PK/PD) in a placebo-controlled study in 24 HIV-infected patients. Bevirimat exhibited linear pharmacokinetics. Volume of distribution at steady state and oral clearance were 13.3 l and 0.17 l/h, respectively, and bevirimat had a prolonged half-life of 60.3 h. The agent dose-dependently inhibited HIV replication, with a maximum inhibition of viral replication of 33.2%, 45.0% and 49.6%, respectively, for doses of 75, 150 and 250 mg. The mean concentration of bevirimat in the effect site inhibiting viral replication by 50% (Ce_{50}) was 59.4 ng/ml and the area under the HIV RNA effect curve (AUEC) was dose-dependent (38, 39).

The PK/PD of multiple doses of bevirimat were also characterized in 32 HIV-infected adults in a phase II clinical study. In this study, the patients received placebo or oral bevirimat once daily at 25, 50, 100 or 200 mg for 10 days. Bevirimat again demonstrated linear pharmacokinetics, with a long mean half-life of 62.7 h. The mean oral clearance of bevirimat was 0.21 l/h. Both AUC and trough concentrations of bevirimat were highly associated with antiviral response. Maximum antiviral effect (E_{max}) for bevirimat was not reached at the highest dose (200 mg) tested (40).

Safety

Bevirimat was well tolerated in preclinical animal studies. No teratogenic effects were observed at doses of 900 mg/kg/day in rats and 300 mg/kg/day in rabbits administered during gestation, well above the anticipated human dose of 200 mg/day (41).

Clinical Studies

The safety and antiviral activity of bevirimat were also reported in the above-mentioned double-blind, placebo-controlled phase II study in HIV-infected patients (40, 42). All doses of bevirimat were generally safe and well tolerated, with no grade 3 or 4 laboratory abnormalities and only mild or moderate adverse events. The study showed

that doses of 100 and 200 mg significantly reduced HIV RNA load compared with placebo. Median decreases on day 11 were 0.17, 0.48 and 1.03 $\log_{10}$ copies/ml for the doses of 50, 100 and 200 mg, respectively. Genotypic data showed no evidence of resistance development to bevirimat.

In the single-dose study in 24 HIV-infected patients, all patients treated with bevirimat (75, 100 or 250 mg) showed reductions in mean viral load compared with placebo. Bevirimat demonstrated dose-dependent antiviral activity, with maximum viral load decreases of 0.27, 0.45 and 0.51 $\log_{10}$ copies/ml, respectively, on doses of 75, 100 and 250 mg, compared to a reduction of 0.17 $\log_{10}$ copies/ml on placebo. No drug-related adverse events were seen. Pre-existing drug resistance mutations in 2 subjects remained susceptible to bevirimat (43).

Drug Interactions

An open-label, randomized study in 48 healthy volunteers examined the PK/PD interactions between bevirimat and atazanavir. Subjects received bevirimat 200 mg once daily for 14 days or atazanavir 400 mg once daily on days 1-21 and bevirimat 200 mg once daily on days 8-21. Bevirimat was generally well tolerated and was not associated with an increase in serum bilirubin, as seen with atazanavir. Co-administration did not significantly increase serum bilirubin levels compared to atazanavir alone and no significant pharmacokinetic interaction between the two anti-HIV agents was seen (19, 44). Also, no clinically relevant interaction between bevirimat and ritonavir has been observed (19).

Source

Panacos Pharmaceuticals, Inc. (US).

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