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DEBIO-025

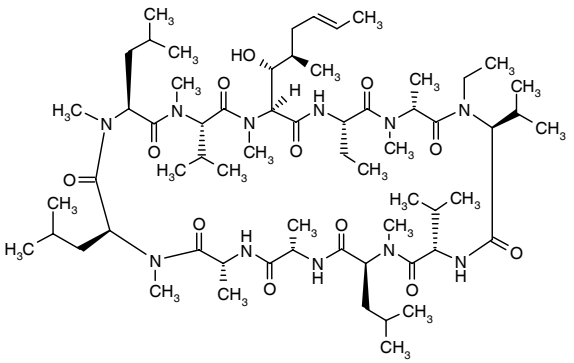
Cyclophilin Inhibitor
Treatment of HCV Infection

UNIL-025

[D-MeAla]^3-[EtVal]^4-cyclosporin A

Cyclo[L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl-(2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl-L-2-aminobutyryl-*N*-methyl-D-alanyl-*N*-ethyl-L-valyl-L-valyl-*N*-methyl-L-leucyl]

InChI=1/C63H113N11O12/c1-26-29-30-40(16)52(75)51-56(79)66-44(27-2)59(82)68(20)43(19)58(81)74(28-3)49(38(12)13)55(78)67-48(37(10)11)62(85)69(21)45(31-34(4)5)54(77)64-41(17)53(76)65-42(18)57(80)70(22)46(32-35(6)7)60(83)71(23)47(33-36(8)9)61(84)72(24)50(39(14)15)63(86)73(51)25/h26,29,34-52,75H,27-28,30-33H2,1-25H3,(H,64,77)(H,65,76)(H,66,79)(H,67,78)/b29-26+/t40-,41+,42-,43-,44+,45+,46+,47+,48+,49+,50+,51+,52-/m1/s1



$C_{63}H_{113}N_{11}O_{12}$
Mol wt: 1216.6378

CAS: 254435-95-5

EN: 383436

Abstract

Debio-025 (UNIL-025) is a first-in-class nonimmunosuppressive cyclophilin inhibitor that has demonstrated in vitro antiviral activity against hepatitis C virus (HCV) and HIV-1 superior to ciclosporin. Antiviral activity has been confirmed in vivo in animal models. Debio-025 has been investigated in several clinical studies in healthy subjects and in patients infected with HCV, HIV or both. The drug was shown to be safe and well tolerated, although some adverse effects have been reported at daily doses of 2400 mg. Debio-025 has been found to reduce HCV viral load in infected patients in the clinical setting, either alone or in combination with interferon alfa. It has also demonstrated potential efficacy in HIV-infected subjects. Combined with the favorable pharmacokinetic and safety profile seen in initial clinical trials, Debio-025 appears to be a good candidate for the treatment of HCV infections, particularly in HIV-1/HCV-coinfected patients.

Synthesis

Acylation of cyclosporin A (CsA, I) with acetic anhydride by means of dimethylaminopyridine (DMAP) in ethyl acetate yields the acylated CsA derivative (II), which by ring-opening treatment with trimethyloxonium tetrafluoroborate in CH_2Cl_2 followed by addition of MeONa/MeOH and sulfuric acid results in the linear undecapeptide (III). Condensation of phenylisothiocyanate with the free α-amino group of the *N*-terminal amino acid of peptide (III) and DMAP in tetrahydrofuran gives the phenylthiocarbamyl derivative (IV), which is submitted to peptide bond cleavage by treatment with trifluoroacetic acid in CH_2Cl_2 to afford the linear acylated decapeptide (V). Coupling of decapeptide (V) with Boc-D-MeAla-EtVal-OH (VI) by means of tetramethylfluoroformamidinium hexafluorophosphate (TFFH) and diisopropylethylamine in dichloromethane gives the protected dodecapeptide (VII), which is reduced with $NaBH_4$ in anhydrous methanol to yield amino alcohol (VIII). Rearrangement of compound (VIII) by treatment with methanesulfonic acid in methanol affords amino ester (IX), which, without purification, is hydrolyzed to the free acid (X) under basic conditions. Finally, this peptide is activated with 7-azabenzotriazol-1-yloxy-tris(pyrrolidino)phosphonium hexafluorophosphate and cyclized by means of collidine in dichloromethane (1). Scheme 1.

Background

Hepatitis C virus (HCV) is a small enveloped RNA virus and the leading cause of chronic liver disease. Current therapy for HCV infection is a combination of pegylated interferon alfa-2A and ribavirin, but the effectiveness of this combination is limited.

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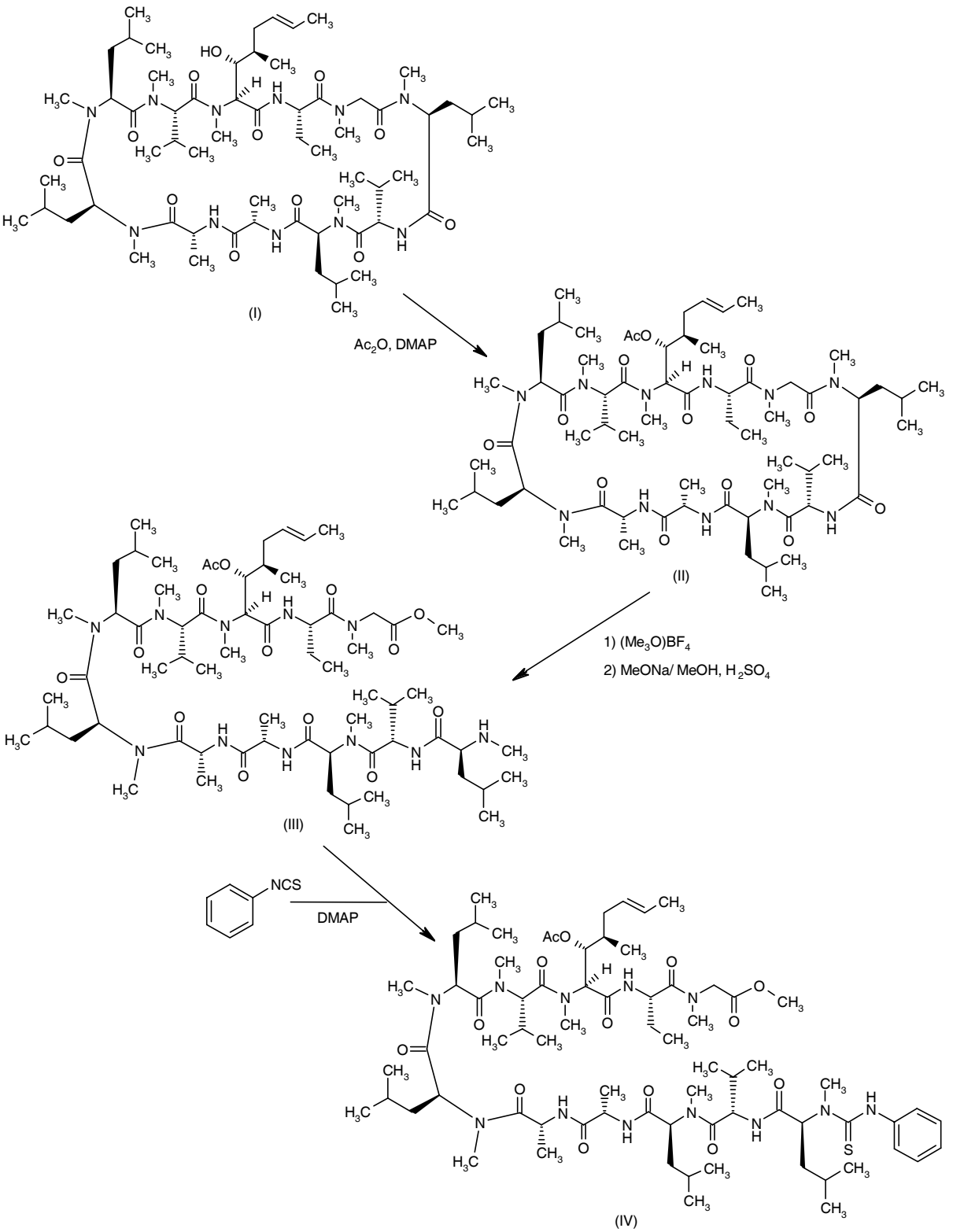
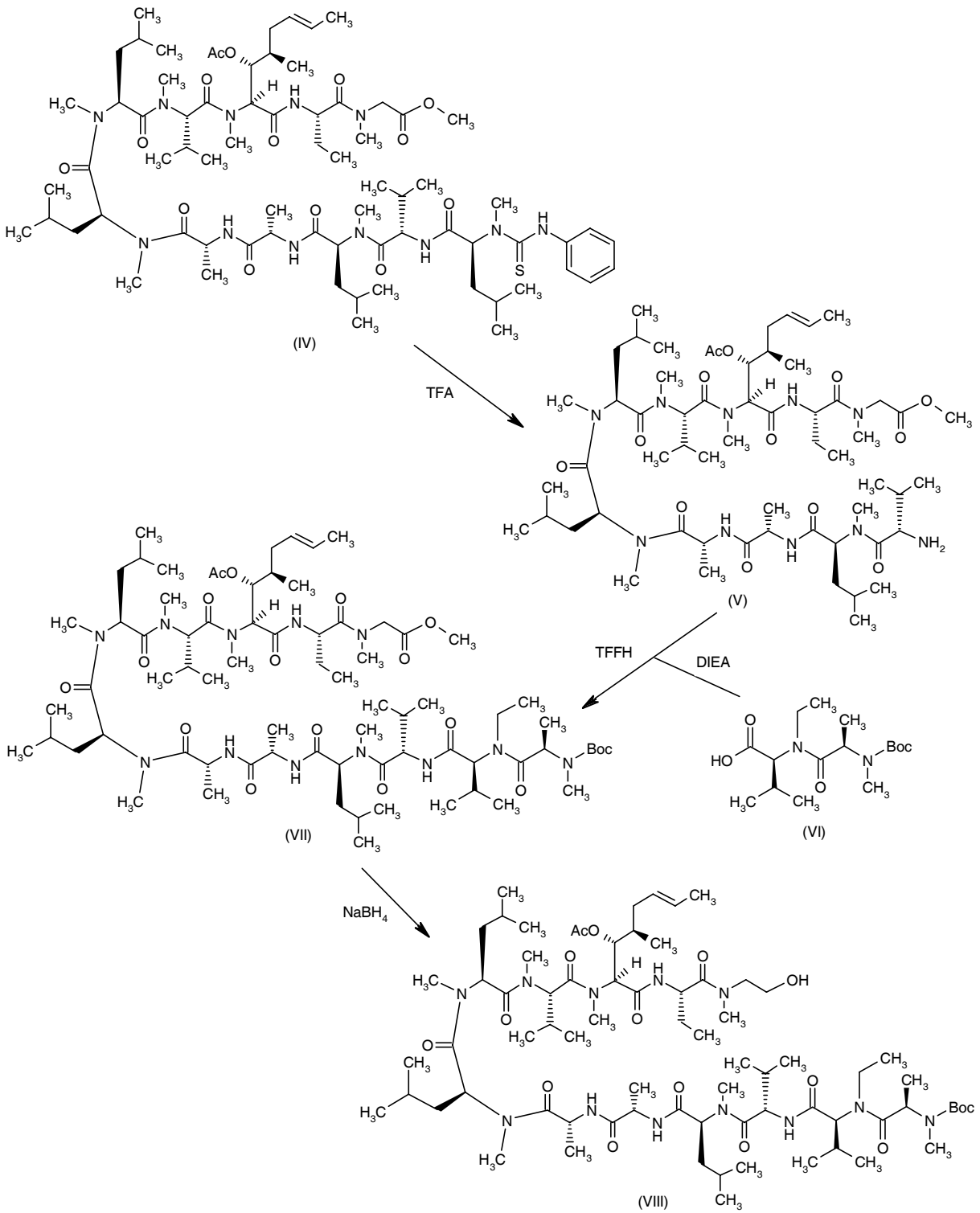
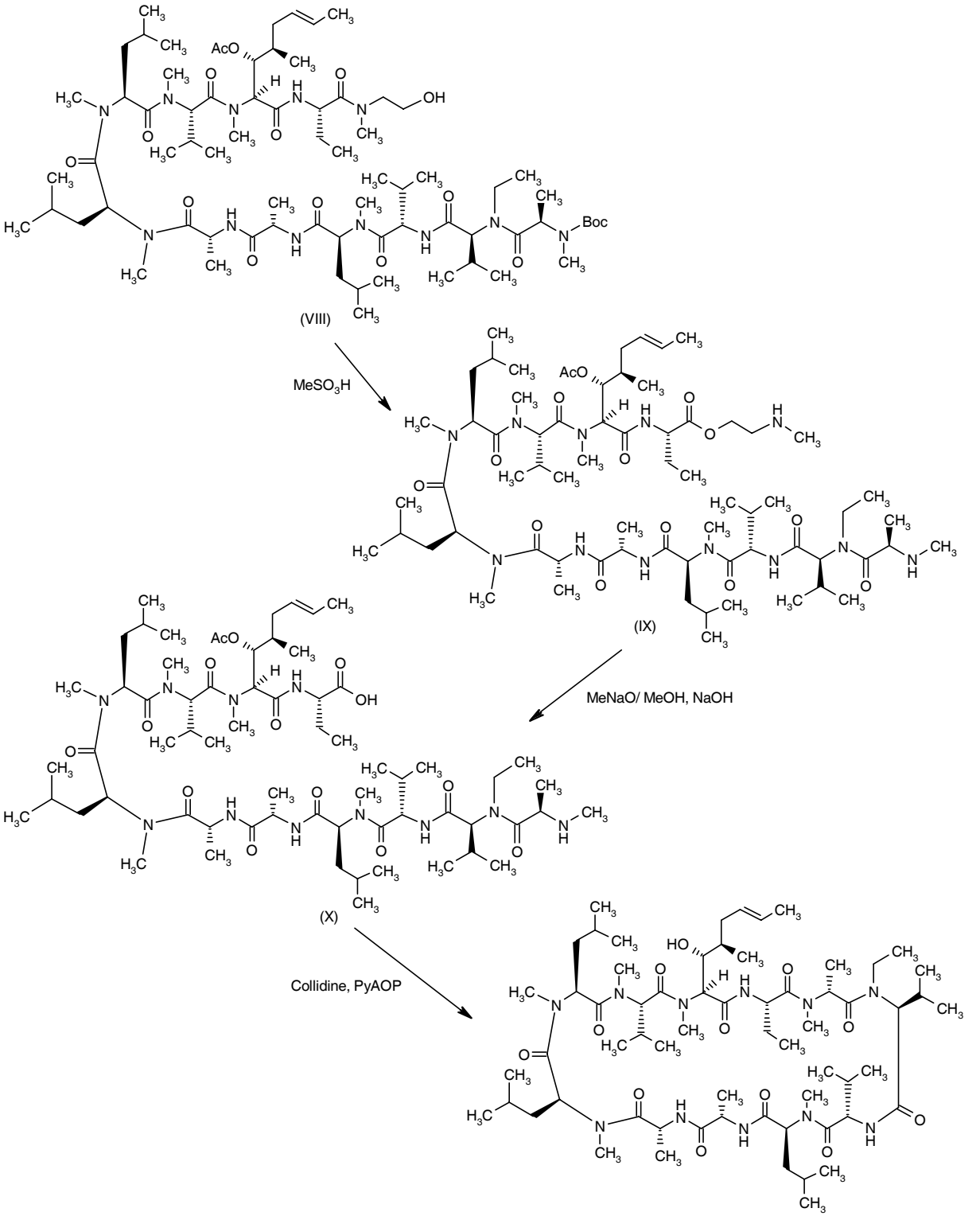
Scheme 1: Synthesis of Debio-025



Scheme 1: Synthesis of Debio-025 (Continued)



Scheme 1: Synthesis of Debio-025 (Continued)



Cyclophilins are abundant intracellular binding proteins that are expressed in many tissue types (2). They catalyze the *cis-trans* interconversion of peptide bond amino-terminal to praline residues, facilitating changes in protein conformation and protein folding, and are involved in several cellular processes such as transcriptional regulation, immune response, protein secretion and mitochondrial function (2, 3). HCV replication depends on cyclophilin and can be reduced in vitro by blocking cyclophilin B function (3). In human immunodeficiency virus (HIV), cyclophilins also act as viral cofactors (4, 5), and the virus recruits cyclophilin A onto its viral capsid to form a protective structure (5).

Ciclosporin is a cyclophilin A inhibitor with potent immunosuppressive activity that has been shown to slightly inhibit HCV and HIV replication (3, 6). Debio-025 is a synthetic ciclosporin analogue with more potent cyclophilin-inhibitory activity and differing from ciclosporin by the substitution of two amino acids. Debio-025 lacks the immunosuppressant effects of ciclosporin and has demonstrated in vitro antiviral activity against HCV and HIV-1 superior to ciclosporin. This antiviral activity has been confirmed in vivo in animal models and in several early-stage clinical studies. Combined with the favorable pharmacokinetic and safety profile emerging from initial clinical trials, Debio-025 therefore appears to be a good candidate for the treatment of HCV infections, particularly in HIV-1/HCV-coinfected patients.

Preclinical Pharmacology

In vitro experiments showed that Debio-025 inhibited HCV replication in both Huh5-2 hepatoma cells containing a subgenomic HCV replicon and in productively HCV-infected cells. Debio-025 reduced HCV viral replication by 50% in Huh5-2 cells at a concentration of 0.03 μg/ml, with no toxic effects on the host cells at concentrations up to 27 μg/ml (7). Several studies demonstrated that both the efficacy and selectivity of Debio-025 were superior of those obtained with ciclosporin (7, 8). The combination of interferon alfa with Debio-025 in the same cellular model resulted in an additive to slightly synergistic antiviral effect (7).

The anti-HCV activity was confirmed in in vivo studies, showing a synergistic interaction between interferon alfa and Debio-025 in chimeric mice bearing HCV-infected human hepatocytes (8).

Debio-025 selectively inhibited the replication of HIV-1 in a $CD4^+$ cell line and in peripheral blood mononuclear cells (PBMCs) in vitro. Potent activity was demonstrated against clinical isolates of various HIV-1 subtypes, including isolates with multidrug resistance to reverse transcriptase and protease inhibitors. Some HIV-1 clinical isolates resistant to Debio-025 and not dependent on cyclophilin A for infection were detected. Simian immunodeficiency virus (SIV) and HIV-2 strains were generally resistant to inhibition by Debio-025, although some notable exceptions of sensitive HIV-2 clinical isolates were detected in this study. In two-drug combination studies, additive inhibitory effects were found for Debio-025 in combination with 19 other drugs used currently for the treatment of HIV infection (9).

Apart from its antiviral activity, Debio-025, like ciclosporin, was also found to be able to block the permeability transition of isolated mitochondria from rat brain in vitro (10). Debio-025 was also shown to inhibit neuronal death in hippocampal slice cultures (11). However, no additional information has been reported regarding the potential neuroprotective effect of the drug.

Pharmacokinetics and Metabolism

Although several early-stage clinical studies have been conducted, there is little information on the pharmacokinetics of Debio-025.

In a phase I study in patients infected with HCV and patients coinfected with HIV and HCV, Debio-025 was given orally at a total dose of 2400 mg/day (1200 mg b.i.d.). The drug was rapidly absorbed and peak plasma levels were reached 2 h after oral administration. The same study showed a terminal half-life of 100 h for the drug (12).

In a 10-day study of daily oral Debio-025 conducted to determine the effects of the drug on HIV-positive antiretroviral-naïve patients, it was reported that pharmacokinetics in plasma and whole blood were best described by a 3-compartment model with saturable binding to blood cells, and were linear in plasma (13).

Safety

Debio-025 has been investigated in several clinical studies in healthy subjects and in patients infected with HCV, HIV or both. The drug was shown to be safe and well tolerated, although some reversible adverse events have been reported at daily doses of 2400 mg.

Daily oral Debio-025 (50, 400 or 1200 mg/kg) administered during 10 days to HIV-positive subjects was safe and well tolerated and no adverse events were reported in the study (13).

In another study, treatment-naïve HCV-infected or HCV/HIV-coinfected patients received 1200 mg of Debio-025 b.i.d. during 15 days. This total daily dose of 2400 mg proved to be generally safe. However, hyperbilirubinemia was observed in 10 patients of the 19 treated with the drug, and led to premature treatment discontinuation in 4. No increase of ALT/AST or γ-GT was observed. A platelet decrease was reported in 3 patients, but was not associated with signs of bleeding. Abnormal bilirubin and platelet levels returned to baseline after the end of treatment (12).

Debio-025 was also safe and well tolerated when administered in combination with interferon alfa at daily doses of 200, 600 and 1000 mg to HCV-infected patients. Treatment lasted 29 days, and at lower doses the safety profile was comparable to placebo. At 1000 mg, 5 of 24 treated patients developed reversible increases in bilirubin resulting in hyperbilirubinemia (14).

Clinical Studies

Debio-025 has been shown to reduce HCV viral load in infected patients in the clinical setting, either alone or in combination with interferon alfa. It has also demonstrated a potential effect in HIV-infected subjects, although more promising results have been seen in HCV/HIV-coinfected patients treated with a combination of Debio-025 and interferon alfa.

A 10-day study was conducted to determine the efficacy of daily oral Debio-025 versus placebo in HIV-positive subjects who had not received prior antiretroviral therapy. Nine patients showed a significant viral load reduction, while 27 patients had no relevant change. The mean reduction was not significantly different between Debio-025 treatment and placebo, and this was not related to drug resistance mutations in the virus (13).

Debio-025 demonstrated a potent anti-HCV effect in patients coinfected with HCV and HIV. The effect of Debio-025 on viral load, as well as its influence on intracellular cyclophilin levels, was investigated in a randomized, double-blind, placebo-controlled study which showed that mean HCV viral load decreased significantly after 14 days of treatment, with an effect against the three HCV genotypes (1, 3 and 4) represented in the study (12).

In 90 treatment-naïve patients with chronic HCV infection, Debio-025 showed an important additive anti-HCV effect when coadministered with interferon alfa (14).

The combination of Debio-025 with interferon alfa and ribavirin is currently being investigated in a phase II clinical study in chronic HCV patients who are nonresponders to standard treatment (15).

Source

Debiopharm SA (CH).

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