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Telaprevir

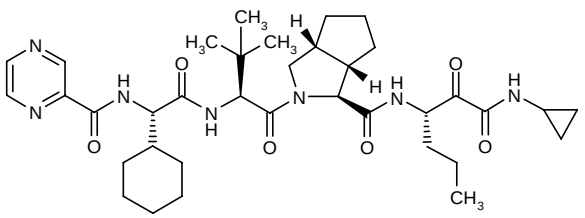
Rec INN; USAN

HCV NS3 Protease Inhibitor
Treatment of Hepatitis C

LY-570310
MP-424
VX-950

(1*S*,3a*R*,6a*S*)-*N*-[1(*S*)-[2-(Cyclopropylamino)oxalyl]butyl]-2-[*N*-(pyrazin-2-ylcarbonyl)-L-cyclohexylglycyl-3-methyl-L-valyl]perhydrocyclopenta[*c*]pyrrole-1-carboxamide

InChI=1/C36H53N7O6/c1-5-10-25(29(44)34(48)39-23-15-16-23)40-33(47)28-24-14-9-13-22(24)20-43(28)35(49)30(36(2,3)4)42-32(46)27(21-11-7-6-8-12-21)41-31(45)26-19-37-17-18-38-26/h17-19,21-25,27-28,30H,5-16,20H2,1-4H3,(H,39,48)(H,40,47)(H,41,45)(H,42,46)/t22-,24-,25-,27-,28-,30+/m0/s1



$C_{36}H_{53}N_7O_6$
Mol wt: 679.8496

CAS: 402957-28-2

EN: 318445

Abstract

Telaprevir is an investigational oral hepatitis C virus (HCV) protease inhibitor in phase II evaluation in combination with pegylated interferon and ribavirin for the treatment of chronically infected patients with genotype 1 hepatitis C. Interim results from a phase II trial indicated that this drug has the potential to shorten the duration of treatment for some patients with genotype 1 HCV. Additional phase II trials involve the treatment of patients who have failed previous interferon-based treatment, as well as treatment in the absence of ribavirin.

Synthesis

Telaprevir can be synthesized as follows:

Hydrogenolysis of the benzyloxycarbonyl protecting group in *N*-Cbz-L-cyclohexylglycyl-L-*tert*-leucine methyl ester (I) in the presence of Pearlman's catalyst in MeOH gives the free dipeptide ester (II), which is acylated with pyrazinecarboxylic acid (III) by means of DCC in dichloromethane/THF to yield the *N*-acyl dipeptide (IV) (1). Alkaline hydrolysis of the methyl ester (IV) followed by coupling of the resulting carboxylic acid (V) with ethyl *cis*-perhydrocyclopenta[*c*]pyrrole-1-carboxylate (VI) by means of DCC provides the acyl tripeptide ester (VII), which is then hydrolyzed to the corresponding carboxylic acid (VIII) upon treatment with NaOH in EtOH (1, 2). Coupling of L-norvaline (IX) with cyclopropylamine (X) in the presence of EDC and *N*-hydroxysuccinimide followed by catalytic hydrogenolysis of the *N*-Cbz group provides *N*-cyclopropyl-norvalinamide (XI) (3). Subsequent condensation of aminoamide (XI) with the *N*-acyl tripeptide (VIII) using either PyBOP or EDC/HOBt gives the tetrapeptide derivative (XII). Finally, oxidation of the secondary alcohol (XII) by means of Dess-Martin periodinane or NaOCl and a catalytic amount of TEMPO furnishes the title α-ketoamide (1-3). Scheme 1.

An alternative route to the precursor *N*-acyl tripeptide (VIII) consists of coupling of *N*-Cbz-L-*tert*-leucine (XIII) with the bicyclic amino ester (XIV) to afford the protected dipeptide (XV), from which the *N*-Cbz group is removed by catalytic hydrogenolysis over Pearlman's catalyst, yielding (XVI). The dipeptide ester (XVI) is then coupled with *N*-Cbz-L-cyclohexylglycine (XVII) to give (XVIII), which is further deprotected by catalytic hydrogenolysis to afford the tripeptide ester (XIX). After acylation of (XIX) with pyrazinecarboxylic acid (III) employing CDI, the resulting *N*-acyl tripeptide *tert*-butyl ester (XX) is treated with HCl in formic acid to provide the target intermediate (VIII) (3). Scheme 2.

The bicyclic amino acid building blocks (VI) and (XIV) can be obtained as follows. Reduction of *N*-Cbz-4-oxo-perhydrocyclopenta[*c*]pyrrole-1-carboxylate (XXI) with $NaBH_4$ in EtOH affords the hydroxy derivative (XXII), which is converted to xanthate (XXIII) by treatment with

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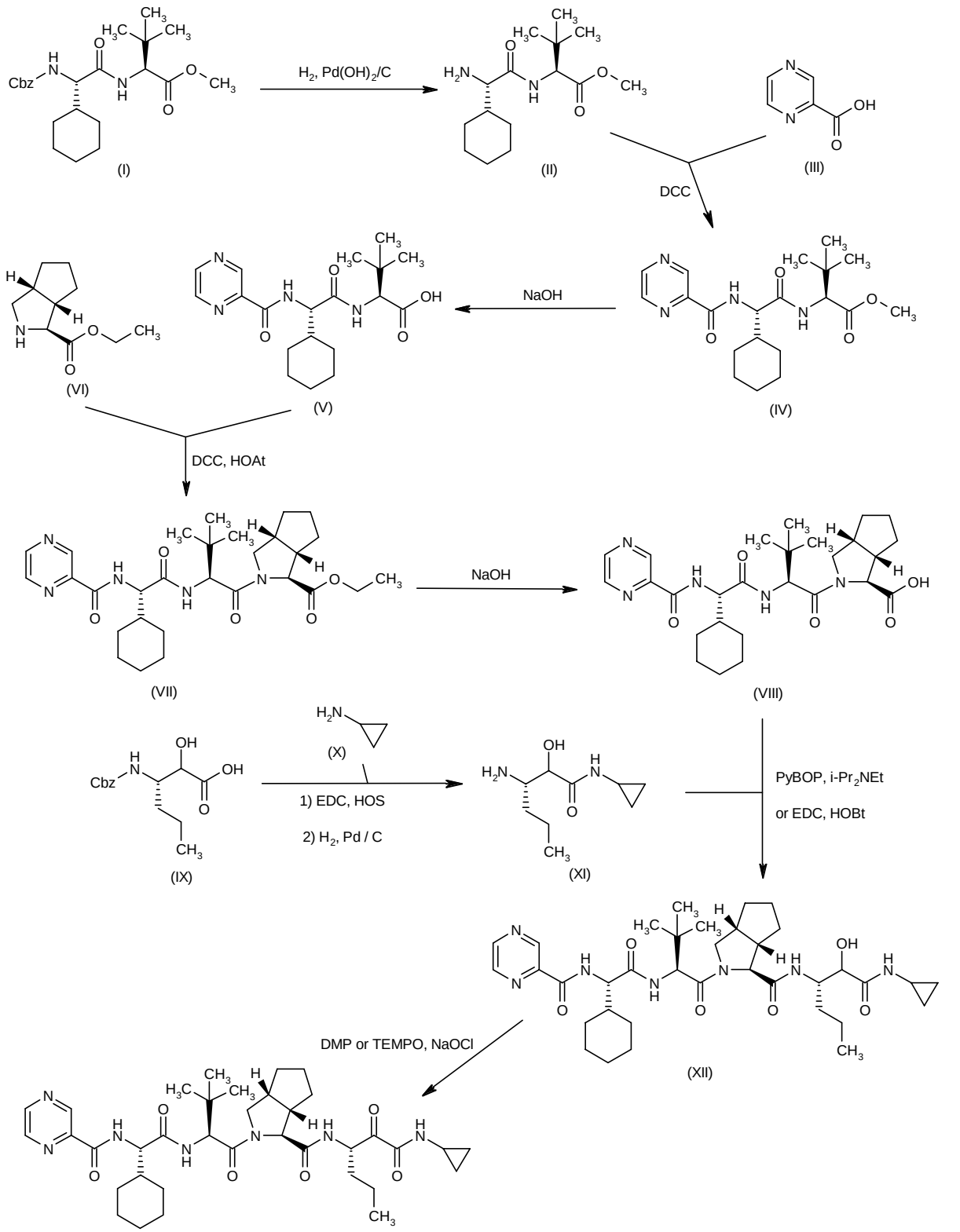
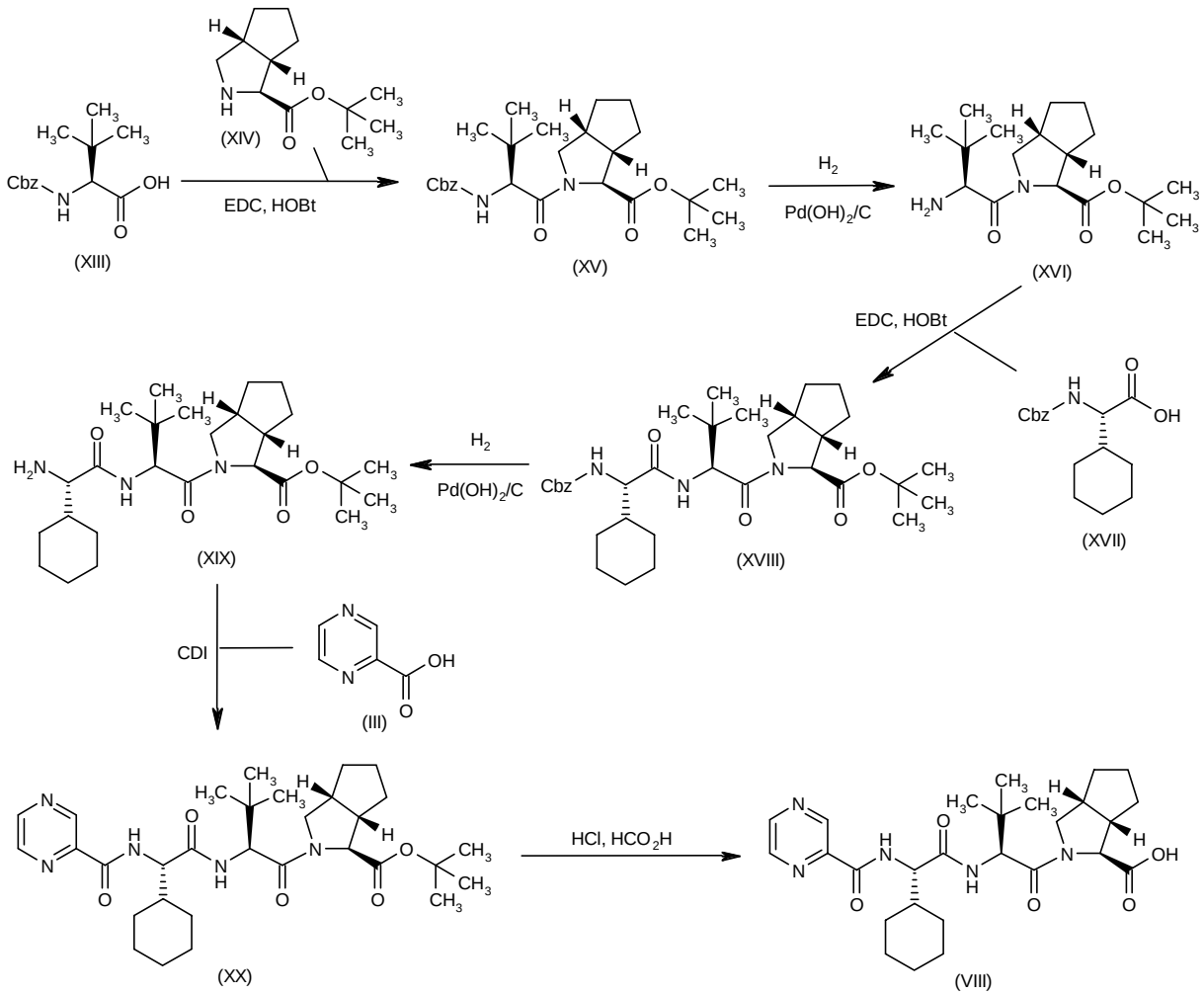
Scheme 1: Synthesis of Telaprevir



Scheme 2: Synthesis of Intermediate (VIII)

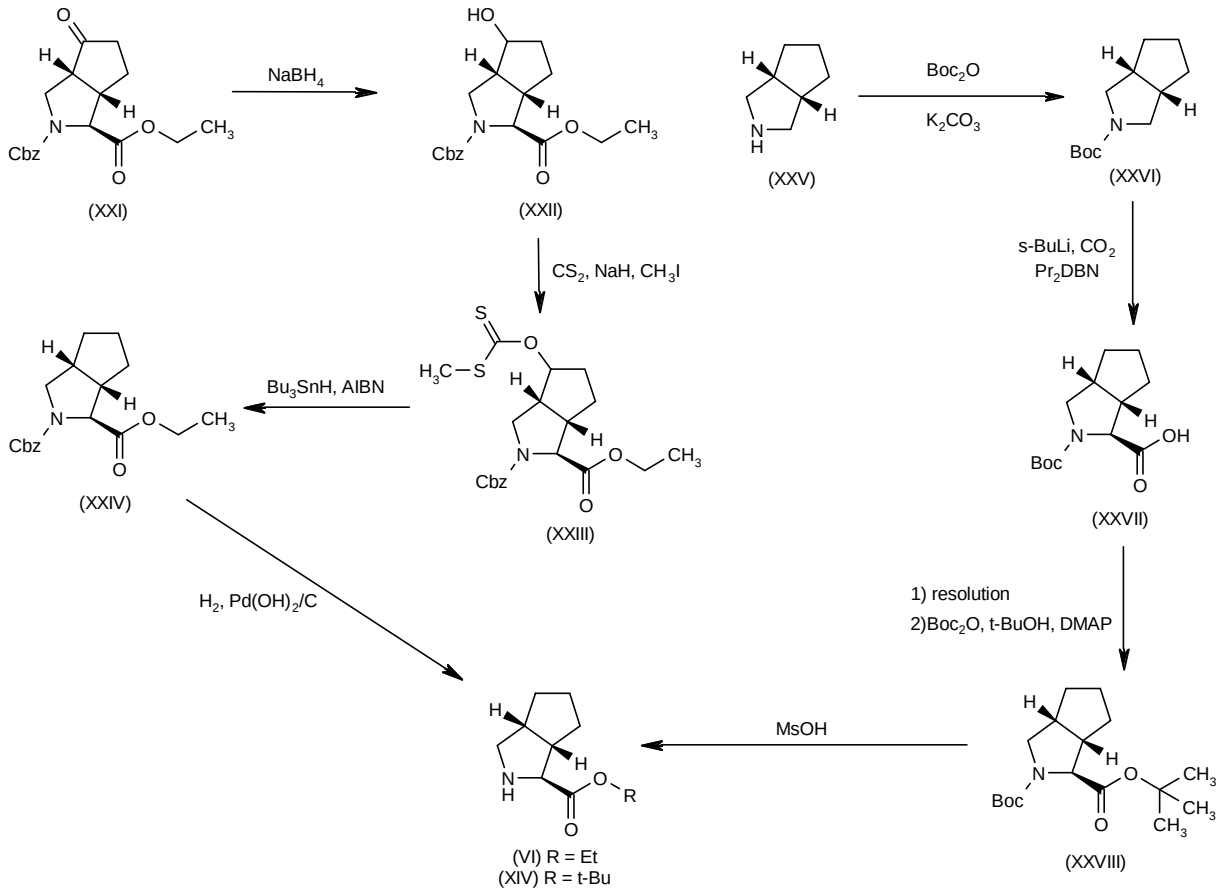


carbon disulfide, iodomethane and NaH in THF. Desulfurization of (XXIII) by means of tributyltin hydride and AIBN in hot toluene affords the *N*-protected bicyclic amino ester (XXIV), which is finally submitted to hydrogenolysis over Pearlman's catalyst to furnish the intermediate (VI) (1). Alternatively, protection of 3-azabicyclo[3.3.0]nonane (XXV) as the *N*-Boc derivative (XXVI) followed by carboxylation with *sec*-butyllithium and CO_2 gas in the presence of 3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane leads to the *N*-protected amino acid (XXVII). After resolution of (XXVII) with either 1,2,3,4-tetrahydro-1(*S*)-naphthylamine or with (*R*)-α-methylbenzylamine, the desired 1(*S*)-amino acid is esterified to (XXVIII) utilizing Boc_2O and DMAP in *t*-BuOH/MTBE. Then, selective Boc group cleavage by means of methanesulfonic acid in THF provides the target intermediate (XIV) (3). Scheme 3.

Background

Hepatitis C virus (HCV) is an RNA virus that causes acute and chronic liver disease which can lead to cirrhosis and hepatic carcinoma. In the U.S., it is estimated that 4.1 million people (1.4% of the population) have been infected with HCV, 10,000-12,000 infected people die each year of HCV-associated liver complications, and over half of all liver transplants (4,000 per year) are attributable to HCV. The incidence of new infections began to rise sharply in the 1960s, peaking in the 1980s at around 130 per 100,000. It has since declined, coincident with the introduction of blood screens and improved practices among those at risk of contracting the disease. However, because disease symptoms usually appear over 20 years after infection, many people do not know they are living with the disease and there is expected to be a sharp rise

Scheme 3: Synthesis of Intermediates (VI) and (XIV)



in the number of adults diagnosed with HCV-attributable hepatitis over the years through 2015 (4-7). The picture worldwide is even bleaker. About 130 million people are infected (2.2% of the population) and the incidence of new infections is 3-4 million per year and increasing, mostly attributable to the use of unscreened blood transfusions and unsterilized injection equipment (6, 7).

The virus is transmitted by blood. Blood transfusion, intravenous drug use, high-risk sex, mother-to-infant transfer and needle stick injury are the most common causes of infection. Immediately following infection, the patient develops acute hepatitis, which is usually mild, and in 20% of cases the immune system is able to fight the infection and it is cleared naturally. In the remaining 80%, the virus evades the immune system and the patient becomes chronically infected (> 6 months). The virus has a dual destructive action in the liver: 1) as it replicates it kills the liver cells; and 2) it triggers an inflammatory response, which adds further to the liver damage. Although infected patients may remain asymptomatic for many years, some 70% of chronically infected patients go on to develop chronic liver disease. Of these, 20-50% develop cirrhosis and 1-5% develop liver cancer over a period of 20-30 years; 25% of hepatocellular cancers are attributable to HCV (4-7).

Current treatment for patients with chronic HCV infection is a combination of pegylated interferon alfa-2a or -2b plus ribavirin. This therapy clears the infection in about 50% of patients with genotype 1 HCV after 48 weeks of therapy, and 75-80% of patients with genotype 2 and 3 HCV after 24 weeks of therapy. Treatment also eliminates the complications associated with infection (4, 8). However, this treatment is not a cure for almost half of infected people, it is prolonged and costly, and there are numerous side effects. For these reasons, alternative treatments are being sought (9, 10).

Unlike interferon alfa and ribavirin, many of the therapeutics currently under development are specifically targeted to the replication cycle of HCV. Telaprevir is a tight-binding inhibitor of the virally encoded NS3/4A serine protease essential for the virus life cycle. NS3 is a multifunctional protease/helicase, and NS4A and zinc are co-

factors required for the protease activity. The protease catalyzes the cleavage of the virally encoded HCV polyprotein to release the functional components required for the viral replication cycle. NS3/4A is also capable of blocking the cellular innate immune response (10-13).

Because HCV has a high mutation frequency and a high replication rate, the viral population in an untreated patient consists of a heterogeneous mix, or 'quasispecies' of HCV viruses. Among these quasispecies there will be some pre-existing variants that are drug-resistant, and while treatment with an antiviral agent such as telaprevir is expected to inhibit the wild-type virus, it will also provide selective pressure for the emergence of the drug-resistant variants. Thus, telaprevir is in development for use in combination with pegylated interferon and ribavirin, which could prevent the emergence of telaprevir-resistant viruses (10, 12).

Preclinical Pharmacology

Telaprevir, a covalent, reversible HCV NS3/4A protease inhibitor, was developed using a structure-based drug design approach (13-16). The compound has a tetrapeptide scaffold designed to mimic one of the natural substrates for the NS3/4A protease, the NS5A/5B cleavage site of genotype 1 HCV. The compound displayed a K_i value of 0.04 μM against genotype 1a NS3/4A protease and a steady-state inhibition constant (K_i*) of 7 nM; inhibition constants of 30-50 and 300 nM, respectively, were obtained against genotype 2a and 3a proteases (13, 17, 18). In another study using patient isolates of NS3/4A protease, there was a < 10-fold variation in the K_i for telaprevir against proteases from HCV genotypes 1a, 1b, 2a, 2b, 3a and 4a (19).

The antiviral properties of telaprevir have been assessed *in vitro* using a subgenomic HCV replicon system. The drug caused a time- and concentration-dependent reduction in viral RNA and protein, with average IC_{50}/IC_{90} values after incubation for 48 h of 0.35/0.83 μM for the reduction of viral RNA; IC_{50} values following 72- and 120-h incubation were 0.210 and 0.139 μM, respectively. These values increased by about 10-fold in the presence of 40% human serum albumin. The compound showed a high selectivity index, with a CC_{50} value in this assay of 83 μM, and in freshly isolated human peripheral blood mononuclear cells (PBMCs) telaprevir had no cytotoxicity at up to the maximum concentration tested (30 μM). Telaprevir also potently inhibited HCV replication in primary human fetal hepatocytes, with an IC_{50} of 0.28 μM for reduction of HCV RNA. Time- and concentration-dependent reductions in HCV RNA were also observed in a 9-day replicon assay, with a 3.3 $\log_{10}$ decrease following incubation with 3.5 μM telaprevir and a 4 $\log_{10}$ decrease following incubation with 7.0 μM. Following 13 days of incubation with 17.5 μM telaprevir in this assay, viral RNA was undetectable (> 4 $\log_{10}$ reduction) and there was no viral rebound after withdrawal of the inhibitor, suggesting the virus had been eliminated from the cells. The combination of telaprevir and interferon alfa was additive to moderately synergistic in inhibiting viral RNA replication, with a 3.5 $\log_{10}$ reduction in viral RNA achieved after 9 days' incubation with 2 μM telaprevir + 10 U/ml interferon alfa. To achieve this level of reduction with either agent alone required 10 μM telaprevir and 250 U/ml interferon alfa. Cytotoxicity was unchanged with the drug combination and the emergence of drug-resistant mutants was suppressed (13, 17, 20).

In human hepatoblastoma HuH6 cells containing a subgenomic HCV replicon, telaprevir inhibited viral replication with an EC_{50} of 1.7 μM and was additive with ribavirin in this model (21).

Telaprevir also inhibited HCV NS3/4A protease *in vivo* using a surrogate SCID mouse model of adenovirus-mediated HCV protease expression in the liver. The mice expressing the active NS3/4A protease developed steatosis and had increased serum secreted alkaline phosphatase (SEAP) levels. Telaprevir produced a reduction in SEAP activity to about 18% of controls at 24 h following 10 and 25 mg/kg p.o. b.i.d., and withdrawal of the drug after 24 h was associated with a rebound of SEAP activity (13, 14, 22, 23).

Using homozygous urokinase plasminogen activator (uPA)-SCID mice, more than half of the mouse liver was repopulated with human hepatocytes to create an *in vivo* chimeric mouse/human HCV model. Upon infection with HCV genotype 1b, these animals maintained a high viral load. Initially, telaprevir given b.i.d. for 7 days or t.i.d. for 3 days led to modest reductions (0.5-1 $\log_{10}$) in viral load. However, when sufficient serum trough concentrations of telaprevir were achieved, viral RNA levels dropped by about 2 $\log_{10}$ in the first 12 h, which corresponds to a rate of 0.15 $\log_{10}$ copies/h, comparable to that seen in clinical trials. This finding implies that it might be possible to estimate effective plasma concentrations in humans by square meter conversion from the animal model. An improved formulation of telaprevir given orally twice daily led to drops in the viral titer of 2-3 $\log_{10}$ in the first 2 days in this model (24).

The HCV subgenomic replicon system was used to select telaprevir-resistant mutants *in vitro*. The dominant variant selected contained an alanine-to-serine substitution at amino acid 156 (A156S) in the NS3 protease domain. The K_i value for the variant protease was 29-fold higher than for the wild-type protease (2.9 μM *vs.* 0.1 μM) in enzyme assays and the IC_{50} in replicon cells was 4.7 μM for the variant, 12-fold higher than for the wild-type replicon (0.40 μM). The A156S variant remained sensitive to ciluprevir (IC_{50} = 7 and 4 nM, respectively, against variant and wild-type replicon cells). Conversely, the dominant ciluprevir-resistant variant (IC_{50} = 5.1 μM *vs.* 0.004 μM against wild-type cells) obtained by the same procedure contained substitutions at aspartate 168 of the protease domain, and these variants remained sensitive to telaprevir (IC_{50} < 0.2 μM) (13, 25-27). Dual telaprevir/ciluprevir-resistant variants were isolated by serial passage of the replicon cultures in the presence of both antivirals. Variants isolated had alanine 156 to valine or threonine (A156V and A156T) substitutions. Both the

A156V and the A156T variants had about 5% of the normal replication capacity of the wild-type replicon, and the catalytic efficiency of the variant proteases was also reduced by 4-7-fold. This implies reduced fitness of the cross-resistant variants. Both of these variant replicons remained sensitive to either interferon alfa or ribavirin (13, 26-28).

Telaprevir not only inhibited the NS3/4A-dependent cleavage of its natural HCV substrate at the 5A/B cleavage site, but also the cleavage of the innate immunity substrate TRIF. Telaprevir-resistant A156T/V variants showed impaired cleavage of HCV 5A/B, TRIF and IPS-1 substrates, consistent with reduced replicative fitness, indicating that the emergence of these variants may not compromise telaprevir's purported ability to restore innate immunity (29).

Pharmacokinetics and Metabolism

Pharmacokinetic parameters of telaprevir in rats, dogs and humans are summarized in Table I.

The moderate to high systemic clearance in rats and dogs together with a steady-state volume of distribution greater than total body water indicated good distribution into tissues. Following oral administration of a suspension of telaprevir in a polymer matrix, the oral bioavailability was determined to be 25% in rats and 40% in dogs. The ratio of telaprevir in liver *versus* plasma was 35:1 after a single oral dose in rats, and 2.3-fold accumulation in liver compared to plasma was seen in dogs, indicating good liver exposure (11, 13, 14). In a study in mice, 1 h after a single oral dose of 10 mg/kg telaprevir, the concentration of the drug in the liver was about 5.7 μM, 6-fold higher than that in the plasma (0.94 μM) and 16-fold higher than the 48-h IC_{50} in the HCV replicon assay (0.35 μM). These ratios increased at higher doses and are consistent with accumulation of the drug in the liver (13, 14).

In a phase I study, 25 healthy male volunteers were randomized to receive single oral doses of 25-1000 mg of telaprevir or placebo. There were no serious adverse events and single doses of telaprevir were well tolerated. Doses of 750 mg or higher gave plasma concentrations of telaprevir that exceeded the IC_{50} for inhibition of HCV replication for 12 h. Given the preferential accumulation of telaprevir in the liver seen in animal models, doses of 750 mg or greater were predicted to provide levels exceeding the IC_{90} for HCV inhibition for 12 h. The elimination half-life ranged from 2 to 6 h, with a median of 4 h at doses of 450 mg and above (30). The results from this and several of the following studies are summarized in Table II.

In part 1 of the randomized, placebo-controlled 2-part phase Ib VX04-950-101 study, three cohorts of 8 healthy subjects received oral doses of telaprevir of 450, 750 and 1250 mg every 8 h for 5 days. Telaprevir was well tolerated and there were no serious adverse events. Good oral bioavailability was observed and steady state was reached in 24-48 h. Average trough levels of drug were approximately 400 ng/ml, therefore exceeding the IC_{50} value for telaprevir in the replicon assay (31).

Clinical Studies

In the second part of the above-mentioned study, 34 patients infected with genotype 1 HCV were randomized to receive oral doses of telaprevir of 450 mg every 8 h, 750 mg every 8 h or 1250 mg every 12 h or matching placebo for 2 weeks. Again, there were no serious adverse events or hematological or cardiac changes. Those receiving placebo showed no change in viral load over the 2-week dosing period. The viral response in those receiving telaprevir could be divided into two phases. In the first phase, the viral load dropped by about 3 log_{10} over the first 2 days of therapy irrespective of the treatment schedule. In the subsequent phase, three response patterns were observed: 1) breakthrough, in which the viral load returned to near pretreatment levels despite treatment; 2) plateau, in which there was no further change in viral load; and 3) continued response, albeit at a slower rate, achieving a > 4 log_{10} decrease in viral load by the end of 2 weeks. These response patterns approximated the dosing groups, but more closely correlated with the plasma trough level of telaprevir. A mean plasma trough level of about 1 μg/ml telaprevir was asso-

Table I: Average plasma pharmacokinetic parameters of telaprevir in different animal models and hepatitis C patients (from Prous Science Integrity®).

Model	Dose	AUC (μg·h/ml)	C_{max} (μg/ml)	C_{min} (μg/ml)	t_{max} (h)	F (%)	Cl (l/h/kg)	V_{ss} (l/h/kg)	$t_{1/2}$ (h)	Ref.
Rats	0.95 mg/kg i.v.	0.30	0.51				3.22	5.81	1.73	17
	4.3 mg/kg i.v.	4.04					1.07	0.54	0.8	18
	30 mg/kg p.o.	2.23	0.49	0.04						18
	40 mg/kg p.o.	3.34	1.55		0.42	25			3.32	17
Dogs	3.5 mg/kg i.v.	1.47	2.38				2.51	1.84	0.93	17
	9.6 mg/kg p.o.	1.64	1.08		0.44	41			3.14	17
Humans	450 mg t.i.d	9.28	1.92	0.78						32, 36
	750 mg t.i.d	9.48	1.72	1.05						32, 36
	1250 mg b.i.d	13.9	2.15	0.68						32, 36

AUC, area under the concentration-time curve; C_{max}, peak plasma concentration; C_{min} trough plasma concentration; t_{max}, time to reach peak plasma concentration; F, bioavailability; Cl, clearance; V_{ss}, steady-state volume of distribution; $t_{1/2}$, elimination half-life.

Table II: Clinical studies of telaprevir (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized	Telaprevir, 25-1000 mg p.o. Placebo	25	Single oral doses of telaprevir were well tolerated and mostly associated with mild adverse events	30
Healthy volunteers	Randomized	Telaprevir, 450 mg p.o. t.i.d. x 5 d Telaprevir, 750 mg p.o. t.i.d. x 5 d Telaprevir, 1250 mg p.o. t.i.d. x 5 d Placebo	24	Telaprevir was well tolerated and associated with mostly mild adverse events in healthy volunteers	31
Hepatitis C	Randomized Open Multicenter	Telaprevir, 750 mg p.o. t.i.d. x 14 d (n=8) Peginterferon alfa-2a, 180 μg s.c. on d 1 & 8 (n=4) Telaprevir, 750 mg p.o. t.i.d. x 14 d + Peginterferon alfa-2a, 180 μg s.c. on d 1 & 8 (n=8)	20	Telaprevir alone or in combination with peginterferon alfa-2a was well tolerated. Telaprevir showed substantial antiviral effects in patients with chronic hepatitis C, especially in combination with peginterferon alfa-2a	42,43,45
Hepatitis C	Open	Telaprevir, 750 mg p.o. t.i.d. + Peginterferon alfa-2a, 180 μg 1x/wk + Ribavirin, 1000-1200 mg/d x 28 d → Peginterferon alfa-2a, 180 μg 1x/wk + Ribavirin, 1000-1200 μg/d	12	The telaprevir, peginterferon alfa-2a and ribavirin combination was well tolerated for 28 days in patients with genotype 1 hepatitis C	48,50
Hepatitis C	Randomized Double-blind	Telaprevir + Peginterferon alfa-2a + Ribavirin Telaprevir + Peginterferon alfa-2a + Placebo	320	This phase II study will evaluate the efficacy of telaprevir plus peginterferon alfa-2a with or without ribavirin in patients with chronic hepatitis C	54
Hepatitis C	Randomized Double-blind	Telaprevir + Ribavirin + Peginterferon alfa-2a Placebo	440	A phase II study was designed to evaluate the efficacy of the telaprevir, ribavirin and peginterferon alfa-2a combination in patients with hepatitis C who had not achieved sustained viral response with a prior course of interferon therapy	55

ciated with the continuous decline response, a mean trough level of 827 ng/ml with the plateau response, and a mean trough level of 719 ng/ml with breakthrough. At 7-10 days after the cessation of dosing, the virus load had begun to rise again in all 28 telaprevir-treated patients, and by long-term follow-up (3-7 months later) it was at or near baseline levels. Blood tests for the liver enzymes aspartate aminotransferase and alanine aminotransferase and for the inflammatory marker neopterin showed a normalization of these markers over the 2-week dosing period, indicating a reduction in liver damage and inflammation (32-36).

In the above study, the initial rapid decline in viral load in response to telaprevir treatment was probably due to the clearance of wild-type virus by telaprevir, but viral breakthrough and plateau responses suggest the selection of telaprevir-resistant variants from pre-existing HCV quasispecies in these patients. Phenotypic analysis demonstrated two classes of telaprevir-resistant variants: T54A, V36A/M, R155K/T and A156S with low-level resistance to telaprevir (< 25-fold increase in IC_{50}) and a relatively high replicative capacity, and A156T/V and double mutants with high-level resistance (> 60-fold increase in IC_{50}) and a lower replicative capacity. After treatment, the low-level resistance, high-fitness mutants, as well as wild-type HCV, predominated in the patient group with viral breakthrough during the treatment period. This patient group had the lowest trough plasma telaprevir levels, ideal conditions for the emergence of this type of variant. The high-level resistance, low-fitness variants predominated in the plateau group with higher trough plasma levels of telaprevir. In the subsequent follow-up periods after treatment withdrawal (3-7 months), the highly resistant, low-fitness variants disappeared rapidly and were replaced by wild-type virus, whereas the low-resistance variants took longer to clear, lingering several months after treatment cessation in those patients who had experienced viral breakthrough. All variants remained sensitive to interferon alfa and ribavirin in the subgenomic HCV replicon assays (33, 37, 38).

Two substudies of this trial examined other markers of HCV infection and hepatitis in telaprevir-treated patients. In one study, a global gene expression profile of whole blood was obtained from healthy and infected subjects to try to identify the transcriptional signature of HCV infection and potential predictors of patient response to drug treatment. Over 250 HCV infection-specific genes were identified, mostly reflecting the host antiviral response, a subset of which had a > 2-fold change in transcription level. Upon treatment, there was a trend towards normalization of the transcriptional profile in those receiving 750 mg telaprevir (39). The size of the perihepatic lymph node has previously been associated with the extent of inflammatory activity in the liver and the antiviral response in patients receiving interferon-based therapy for chronic HCV infection. In a prospective analysis of the perihepatic lymph

node volume in 19 patients in the VX04-950-101 study, those receiving telaprevir had a significant decrease in lymph node volume by day 14 (from 1.26 ml to 0.76 ml), whereas those receiving placebo did not (40, 41).

VX04-950-103 was a phase I study of telaprevir in combination with pegylated interferon in 20 treatment-naïve patients with genotype 1 HCV. Patients were randomized to receive pegylated interferon alfa-2a (Pegasy®, 180 μg s.c. once weekly; n=4), telaprevir (loading dose of 1250 mg p.o., then 750 mg p.o. every 8 h; n=8) or pegylated interferon + telaprevir (n=8) for 2 weeks. At the end of the 2-week period, patients were offered standard pegylated interferon plus ribavirin treatment and monitoring continued. The majority of adverse events were mild and there were no serious events or premature discontinuations. At day 15, the median change in HCV RNA from baseline was –1.09 $\log_{10}$ for the pegylated interferon group, –3.99 $\log_{10}$ for the telaprevir group and –5.49 $\log_{10}$ for the telaprevir + pegylated interferon group. As seen previously, the viral response of those receiving telaprevir could be divided into two phases: an initial rapid decline of viral load followed by a subsequent period of either breakthrough or continued decline. Four of 8 patients in the telaprevir group had viral breakthrough, and by day 15 the highly telaprevir-resistant double mutants V36M/A/R155K/T predominated. There were no breakthrough events and virus load continued to decline in all patients in the telaprevir + pegylated interferon group, despite the presence of the highly telaprevir-resistant A156V/T variants in 2 of these patients early on in the study, indicating that the combination suppressed the growth of this variant. At week 24, HCV RNA was undetectable in all of the 15 patients treated with telaprevir in the initial dosing period and who had opted to follow-on with standard pegylated interferon + ribavirin therapy. Follow-up studies will continue for up to 48 weeks in this trial (42-46). Baseline levels of alanine aminotransferase were elevated in 12 of 20 patients and decreased in all three treatment groups, indicating reduced liver damage with treatment. Baseline neopterin levels were elevated in 15 of 20 patients and decreased in the telaprevir group but increased in the patients receiving pegylated interferon, consistent with the action of interferon, and indicating that telaprevir does not interfere with this activity (47).

Study VX05-950-102 was a 4-week, nonrandomized, open-label, uncontrolled phase II study of telaprevir in combination with pegylated interferon alfa-2a (Pegasys®) and ribavirin (Copegus®) in 12 treatment-naïve HCV patients. Patients received telaprevir (750 mg every 8 h) + pegylated interferon (180 μg weekly) + ribavirin (1 or 1.2 g/day). After 28 days, the patients were switched to standard therapy with pegylated interferon + ribavirin. This treatment schedule was well tolerated and there were no serious adverse events. Viral RNA was undetectable in all patients at the end of the treatment period, despite the presence of viral variants early on in 2 patients. At week 12 of follow-on therapy, virus was undetectable in 11 of 12 patients (48-50).

PROVE 1 (VX05-950-104) is a randomized, double-blind, placebo-controlled, parallel-assignment phase II study of telaprevir in combination with pegylated interferon alfa-2a (Pegasys®) and ribavirin (Copegus®) in patients with genotype 1 HCV who have not received prior treatment. A total of 250 patients were randomized to 1 of 4 treatment arms: those in arm A (n=75) received placebo + pegylated interferon (180 μg once weekly) + ribavirin (1 or 1.2 g/day) for 12 weeks, and then continued on pegylated interferon + ribavirin for a total of 48 weeks; those in arms B, C and D received telaprevir (750 mg every 8 h) + pegylated interferon + ribavirin for 12 weeks, followed by standard therapy for 0, 12 and 36 weeks, respectively. In genotype 1 HCV infections, a lack of rapid viral response (defined in this study as < 30 and < 10 IU/ml at the end of 4 weeks of dosing) is associated with a failure to achieve a sustained viral response. In a planned interim analysis at the end of the 12-week telaprevir treatment period, 88% and 79%, respectively, of those receiving telaprevir had viral RNA levels of < 30 and < 10 IU/ml after 4 weeks *versus* 16% and 11%, respectively, in the control group. Viral breakthrough occurred in 7% of patients receiving telaprevir, all but 1 case of which occurred in the first 4 weeks of treatment. Of 17 patients in arm D for whom data were available, 9 had undetectable HCV at week 4, which was maintained at week 12; 4 discontinued due to adverse events, and 4 did not achieve the initial 4-week rapid response and were assigned to continue on pegylated interferon + ribavirin at week 12. Six of the 9 rapidly responding patients in arm D remained HCV-negative 20 weeks after the cessation of all treatment, indicating the potential to shorten the treatment duration to 24 weeks in genotype 1 HCV patients. The total incidence of adverse events was similar for placebo and telaprevir treatment groups (75% *vs.* 80%). Study discontinuations were more frequent among those receiving telaprevir (11% *vs.* 3% for the placebo group), with discontinuations in the telaprevir treatment arms attributable to an increased incidence of rash, gastrointestinal events and anemia (51-53).

PROVE 2 (VX05-950-104EU) and PROVE 3 (VX06-950-106) are phase II studies designed to evaluate the safety and efficacy of different durations of telaprevir-based therapies in patients chronically infected with HCV genotype 1. PROVE 2 will enroll approximately 240 treatment-naïve patients and will evaluate telaprevir + pegylated interferon with or without ribavirin (54), and PROVE 3 will evaluate telaprevir + pegylated interferon + ribavirin in more than 440 patients who have failed previous interferon-based therapies (55). The phase II VX06-950-012 study is investigating the safety and pharmacokinetics of multiple doses of telaprevir in patients with moderate and severe hepatic impairment and who are negative for HCV, HBV and HIV (56).

Drug Interactions

Telaprevir is primarily metabolized by the cytochrome P-450 CYP3A system, with approximately 25-30% of the

parent drug remaining after 30-min incubation with rat or human liver microsomes. Co-incubation of telaprevir with 4 μM of the CYP3A inhibitor ritonavir resulted in complete inhibition of the metabolism of telaprevir, demonstrating the potential for pharmacokinetic enhancement by ritonavir. In rats, oral co-administration of 5 mg/kg telaprevir and 5 mg/kg ritonavir enhanced the AUC_{0-8h} by > 15-fold and the plasma concentration at 8 h by > 50-fold. A pharmacokinetic model of ritonavir-boosted telaprevir in humans predicted that a combination of 250 mg telaprevir + 100 mg ritonavir twice daily would achieve the same trough plasma concentrations as 750 mg telaprevir t.i.d. (57, 58).

Sources

Vertex Pharmaceuticals, Inc. (US); Janssen Pharmaceutica (Johnson & Johnson) holds development and marketing rights in Europe, South America, the Middle East, Africa and Australia, and Mitsubishi Pharma holds rights in Japan and certain Far East countries.

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