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BOCEPREVIR

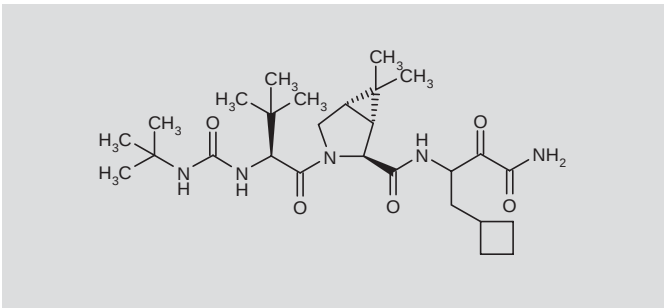
Rec INN; USAN

NS3 Protease Inhibitor
Treatment of Chronic Hepatitis C

SCH-503034

(1*R*,2*S*,5*S*)-3-[*N*-(*N*-*tert*-Butylcarbamoyl)-3-methyl-L-valyl]-*N*-(2-cyclobutyl-1-oxamoylethyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

InChI: 1S/C27H45N5O5/c1-25(2,3)20(30-24(37)31-26(4,5)6)23(36)32-13-15-17(27(15,7)8)18(32)22(35)29-16(19(33)21(28)34)12-14-10-9-11-14/h14-18,20H,9-13H2,1-8H3,(H2,28,34)(H,29,35)(H2,30,31,37)/t15-,16?,17-,18-,20+/m0/s1



$C_{27}H_{45}N_5O_5$
Mol wt: 519.6767
CAS: 394730-60-0
EN: 405424

ABSTRACT

Boceprevir (SCH-503034) is a potent, orally bioavailable inhibitor of the hepatitis C virus (HCV) NS3 protease. Several studies have demonstrated that boceprevir is well tolerated when given in combination with peginterferon and ribavirin. It has shown clinical efficacy (sustained virological response) in naïve patients and in nonresponders to the combination peginterferon/ribavirin when combined with these two compounds. As with other targeted antiviral compounds, resistant genetic variants of the virus emerge during boceprevir treatment, and this can be substantially decreased by combination with antivirals with unrelated mechanisms of action. Boceprevir is currently in phase III clinical trials for the treatment of chronic HCV genotype 1 in combination with peginterferon alfa-2b and ribavirin in patients who have demonstrated interferon responsiveness but who failed to achieve sustained virological response on prior treatment with any combination of peginterferon alfa and ribavirin, and in previously untreated patients. In 2008 the compound received fast track designation from the FDA for the treatment of chronic HCV genotype 1 virus infection in these resistant patients.

SYNTHESIS

Boceprevir can be prepared by several related synthetic strategies.

Coupling of dipeptide derivative (I) with 3-amino-4-cyclobutyl-2-hydroxybutyramide hydrochloride (II) using EDC by means of NMM in DMF/CH_2Cl_2 gives the α-hydroxy amide (III) (1-4), which is finally oxidized under modified Swern conditions (DMSO, EDC and dichloroacetic acid in toluene) (1-4) or by means of NaOCl and catalytic TEMPO in the presence of KBr and NaOAc/AcOH in MTBE/H_2O (5). Scheme 1.

In a modified procedure, treatment of acid (I) with *N,N*-dicyclohexylamine (IV) gives the corresponding salt (V), which is then coupled with compound (II) using EDC by means of either HOBt and NMM or DIEA in EtOAc, 2-hydroxypyridine in DMF/MTBE, DMAP in EtOAc/DMF, or 1,3,5-trimethoxy-2,4,6-triazine (TMT) and NMM in EtOAc/DMF to afford compound (III). Similarly, treatment of dimethylcyclohexylamine salt (V) with carbonyldiimidazole (CDI) in the presence of DIEA in DMF produces the corresponding acyl imidazolide, which, without isolation, is then coupled with compound (II) to furnish adduct (III) (6). Scheme 1.

In a related strategy, boceprevir is obtained by coupling of dipeptide derivative (I) with 3-amino-4-cyclobutyl-2-oxobutyramide (VI) using EDC, HOBt and NMM in acetonitrile or via activation of (I) as the mixed anhydride with isobutyl chloroformate and NMM in EtOAc (7). Scheme 1.

The precursor (I) is prepared as follows.

After protection of L-*tert*-leucine (VIIa) as the corresponding silyl ester (VIII) with TMSCl by means of HMDS or Et_3N in refluxing CH_2Cl_2, condensation with *tert*-butyl isocyanate (IX), followed by acidic work up leads to urea derivative (X) (8). Subsequent coupling of carboxylic acid (X) with methyl (1*R*,2*S*,5*S*)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate HCl salt (XI) in the presence of EDC, HOBt and 2,6-lutidine in acetonitrile yields the dipeptide ester (XII) (6, 7), which is finally hydrolyzed with LiOH in THF/H_2O

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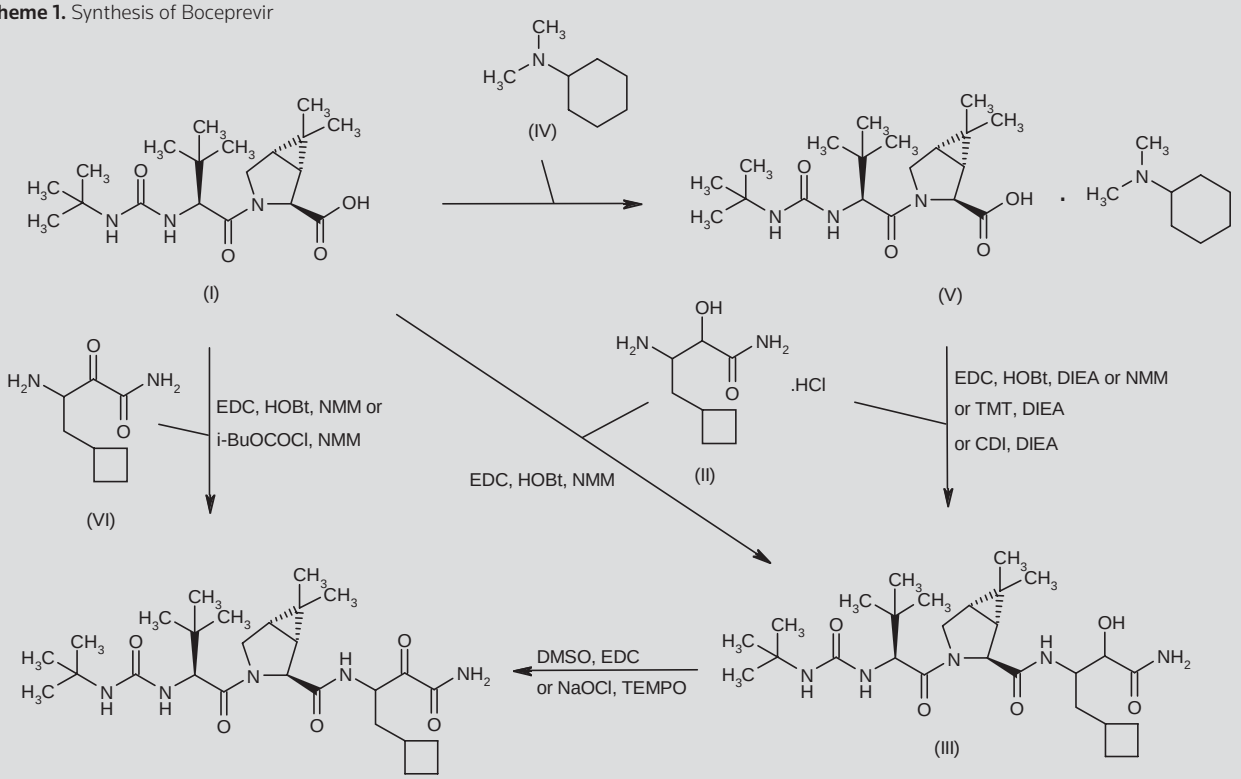
Scheme 1. Synthesis of Boceprevir



(1-4, 6, 7) and optionally purified via its α-methylbenzylamine salt (5). Scheme 2.

Alternatively, coupling of *N*-Boc-L-*tert*-leucine (VIIb) with the bicyclic amino ester (XI) in the presence of BOP reagent and NMM in CH_2Cl_2/DMF affords the *N*-Boc dipeptide (XIII), which is then deprotected by means of HCl in dioxane to give compound (XIV) (1, 4 ,6). Finally, intermediate (XIV) is condensed with *tert*-butyl isocyanate (IX) in CH_2Cl_2 to give the urea compound (XII). Scheme 2.

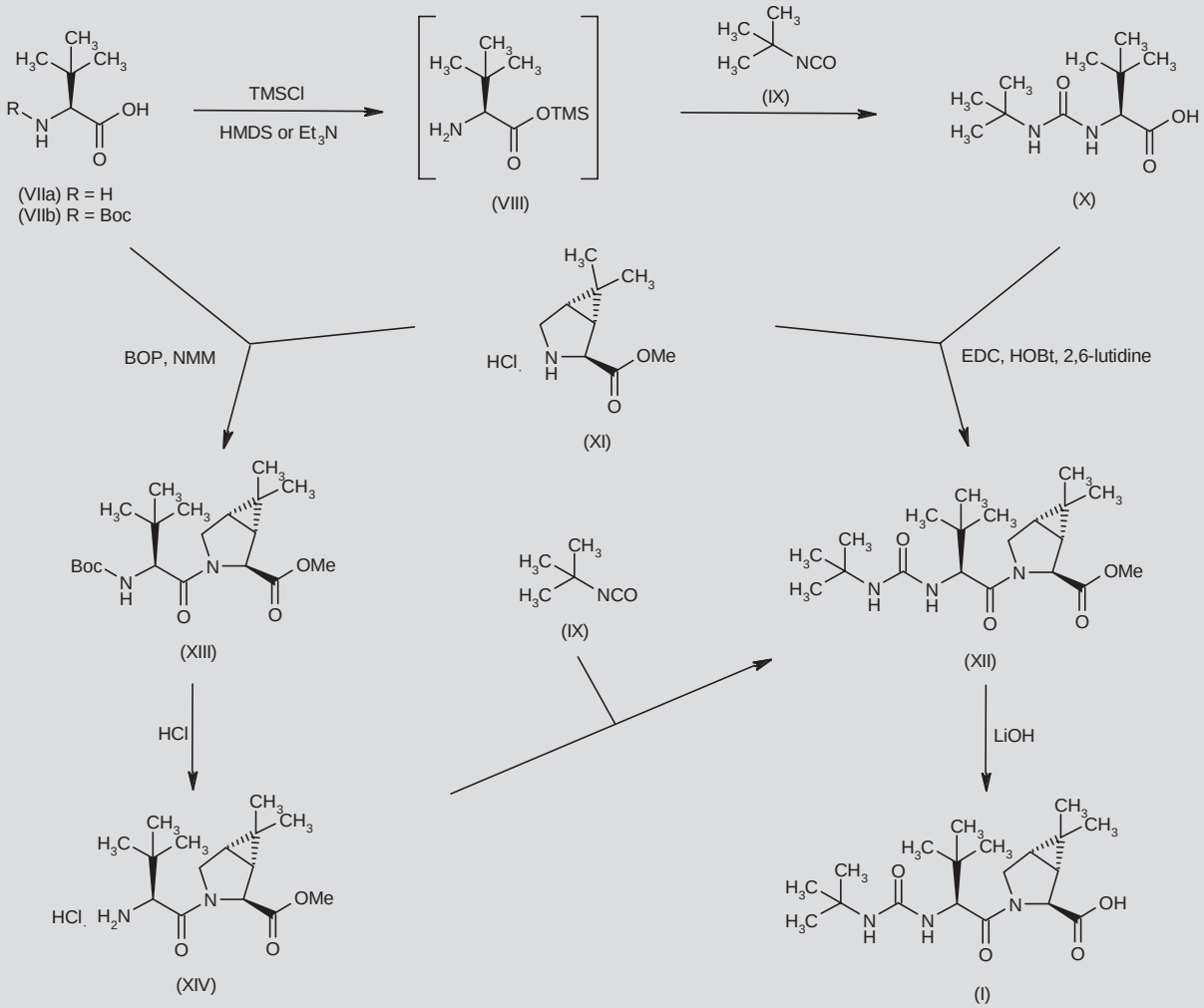
The aminobutyramide building blocks (II) and (VI) are obtained as follows.

Alkylation of the benzophenone imine of ethyl glycinate (XV) with bromomethylcyclobutane (XVI) by means of *t*-BuOK in THF at –78 °C, followed by acidic hydrolysis of the imine intermediate (XVII) gives 3-cyclobutyl-DL-alanine ethyl ester (XVIII). Subsequent protection of the amino ester (XVIII) with Boc_2O in CH_2Cl_2 yields the *N*-Boc derivative (XIX), which upon alkaline hydrolysis of its ethyl ester group with LiOH in THF/H_2O gives the *N*-Boc-protected amino acid (XX). After coupling amino acid (XX) with *N,O*-dimethylhydroxylamine in the presence of BOP and NMM in CH_2Cl_2, the resulting Weinreb amide (XXI) is reduced to aldehyde (XXII) using $LiAlH_4$ in cold THF. Aldehyde (XXII) is then reacted with 2-hydroxyisobutyronitrile and Et_3N to give cyanohydrin (XXIII), which by treatment with methanolic hydrochloric acid yields amino ester (XXIV), and subsequently reprotection with Boc_2O leads to the *N*-Boc-protected amino ester (XXV). Hydrolysis of methyl ester (XXV) using LiOH followed by coupling of the resulting carboxylic acid (XXVI) with NH_4Cl in the presence of EDC, HOBt and NMM in DMF affords carboxamide (XXVII) (1-4, 6). Alternatively, carboxamide (XXVII) also results from direct hydrolysis of nitrile (XXIII) using LiOH and H_2O_2 in MeOH (4). Finally, acidic *N*-Boc group cleavage in compound (XXVII) provides the key amino hydroxyamide intermediate (II) (1-4). The analogous amino ketoamide (VI) is obtained by Swern oxidation of alcohol (XXVII) with DMSO and EDC in the presence of dichloroacetic acid in *i*-PrOH/EtOAc followed by acidic Boc group cleavage with HCl/*i*-PrOH at 40-50 °C (7). Scheme 3.

Alternatively, intermediate (XXVII) can be prepared as follows.

Oxidation of cyclobutanemethanol (XXVIII) with NaOCl and catalytic TEMPO by means of KBr and $NaHCO_3$ in CH_2Cl_2/H_2O gives cyclobutanecarboxaldehyde (XXIX), which is then condensed with nitromethane in the presence of Et_3N in toluene to yield the nitro alcohol (XXX). Subsequent treatment of alcohol (XXX) with acetic anhydride in the presence of DMAP furnishes a mixture of the acetate ester (XXXI) and the dehydration compound (2-nitrovinyl)cyclobutane (XXXII), which can also be obtained as the only reaction product by dehydration of nitro alcohol (XXX) with MsCl in the presence of Et_3N. Reduction of the mixture of compounds (XXXI) and (XXXII) or the nitro olefin (XXXII) by catalytic hydrogenation over Pd/C in MeOH optionally in the presence of Et_3N, or with $NaBH_4$ in PEG-400/H_2O or *t*-BuOH, affords (2-nitroethyl)cyclobutane (XXXIII),

Scheme 2. Synthesis of Intermediate (I)



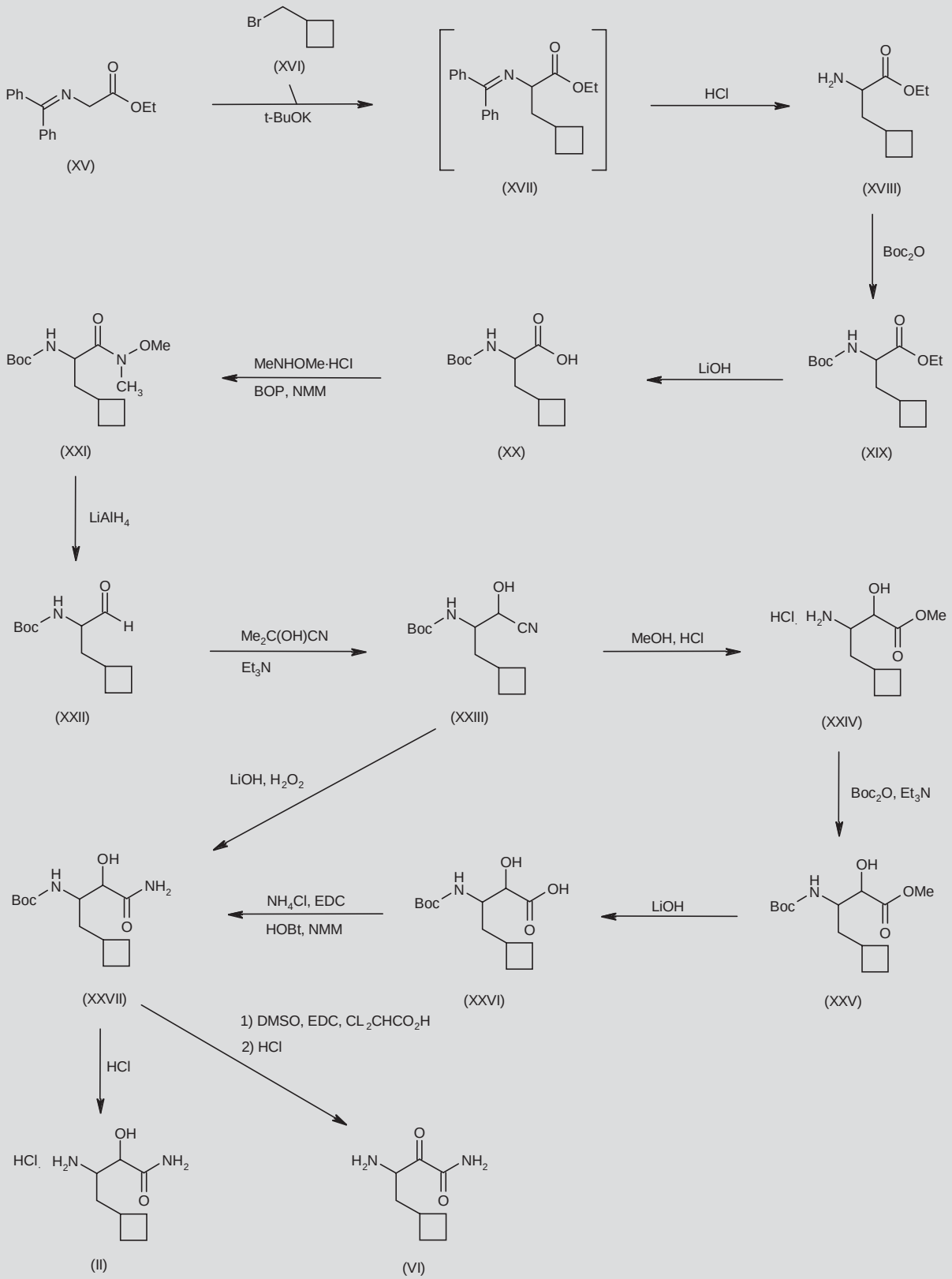
which is condensed with glyoxylic acid (XXXIV) in the presence of Et_3N to yield the nitro hydroxy acid (XXXV). Then, compound (XXXV) is reduced with H_2 over Pd/C in MeOH and esterified with MeOH and *p*-TsOH·H_2O to give amino ester (XXXVI). Finally, aminolysis of methyl ester (XXXVI) with NH_3 and NH_4OH in MeOH followed by *N*-protection by means of Boc_2O and K_2CO_3 in MeOH/H_2O yields intermediate (XXVII) (9). Scheme 4.

The bicyclic amino ester (XI) can be obtained by several alternative methods.

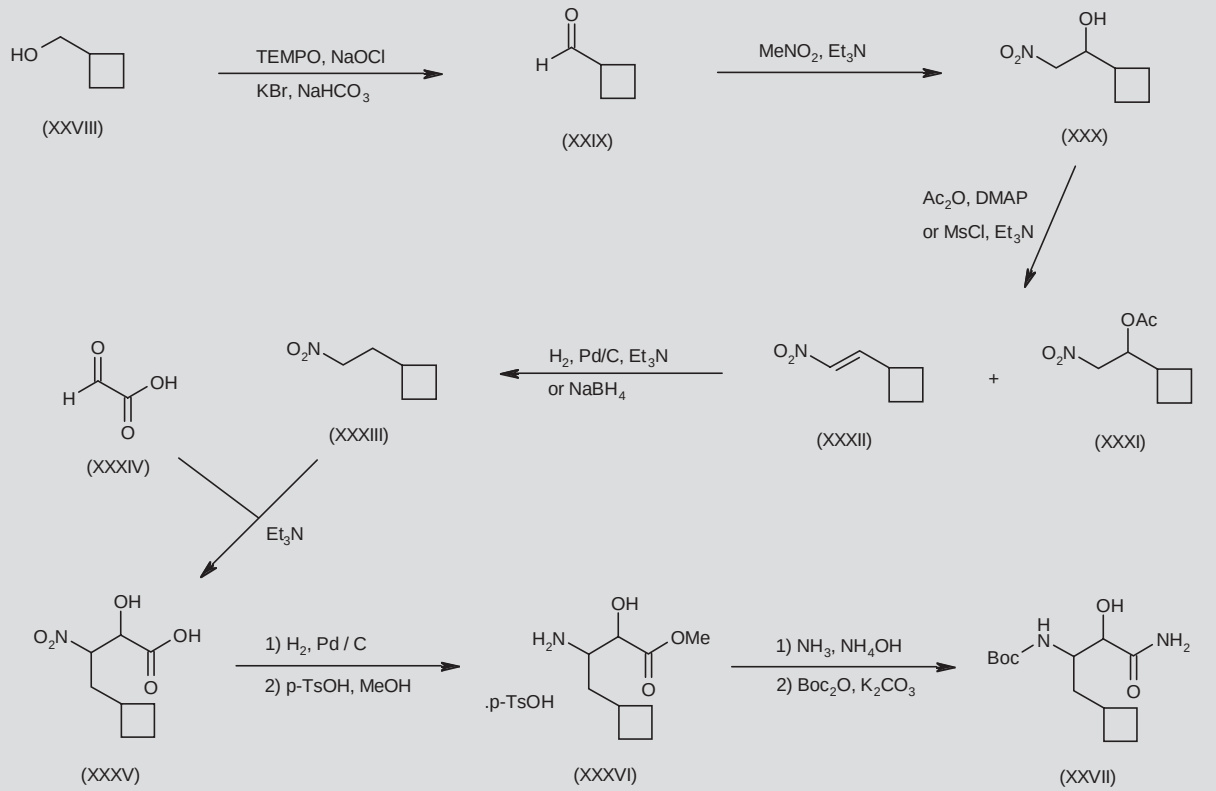
Dehydrogenation of *2*(*R*)-phenylperhydropyrrolo[1,*2-c*]oxazol-4-one (XXXVII) by α-selenylation with PhSeCl in the presence of KHMDS and TMSCl in THF, followed by oxidation with H_2O_2 in pyridine (4) or EtOAc (10) and elimination of the selenoxide intermediate produces the unsaturated analogue (XXXVIII) (4, 10), which by cyclopropanation by means of isopropyl trimethylphosphonium bromide and BuLi in THF affords the tricyclic compound (XXXIX). Reductive ring opening of intermediate (XXXIX) by means of $LiAlH_4$ in refluxing THF produces the *N*-benzylprolinol (XL), which is debenzylated to the prolinol (XLI) by catalytic hydrogenation over Pd/C in AcOH/EtOAc. After protection of amine (XLI) with Boc_2O in CH_2Cl_2, the resulting *N*-Boc-cyclopropaprolinol (XLII) is subjected to Jones oxidation to furnish carboxylic acid (XLIII). Subsequent esterification of acid (XLIII) with (trimethylsilyl)diazomethane in toluene/MeOH affords the *N*-Boc-cyclopropaproline methyl ester (XLIV), which is finally deprotected with HCl in dioxane (4). Scheme 5.

In an alternative method to intermediate (XI), dehydration of caronic acid (XLV) by heating with Ac_2O and H_2SO_4 in toluene at 190 °C produces caronic anhydride (XLVI) (11), which is then condensed with benzylamine in *tert*-butyl methyl ether at 170-180 °C to yield the bicyclic imide (XLVII). Subsequent reduction of imide (XLVII) with $LiAlH_4$ in refluxing THF followed by debenzylation of the obtained pyrrolidine derivative (XLVIII) by catalytic hydrogenation over

Scheme 3. Synthesis of Building Blocks (II) and (VI)



Scheme 4. Alternative synthesis of Intermediate (XXVII)



Pd/C in AcOH furnishes 6,6-dimethyl-3-azabicyclo[3.1.0]hexane (XLIX) (12). Scheme 6.

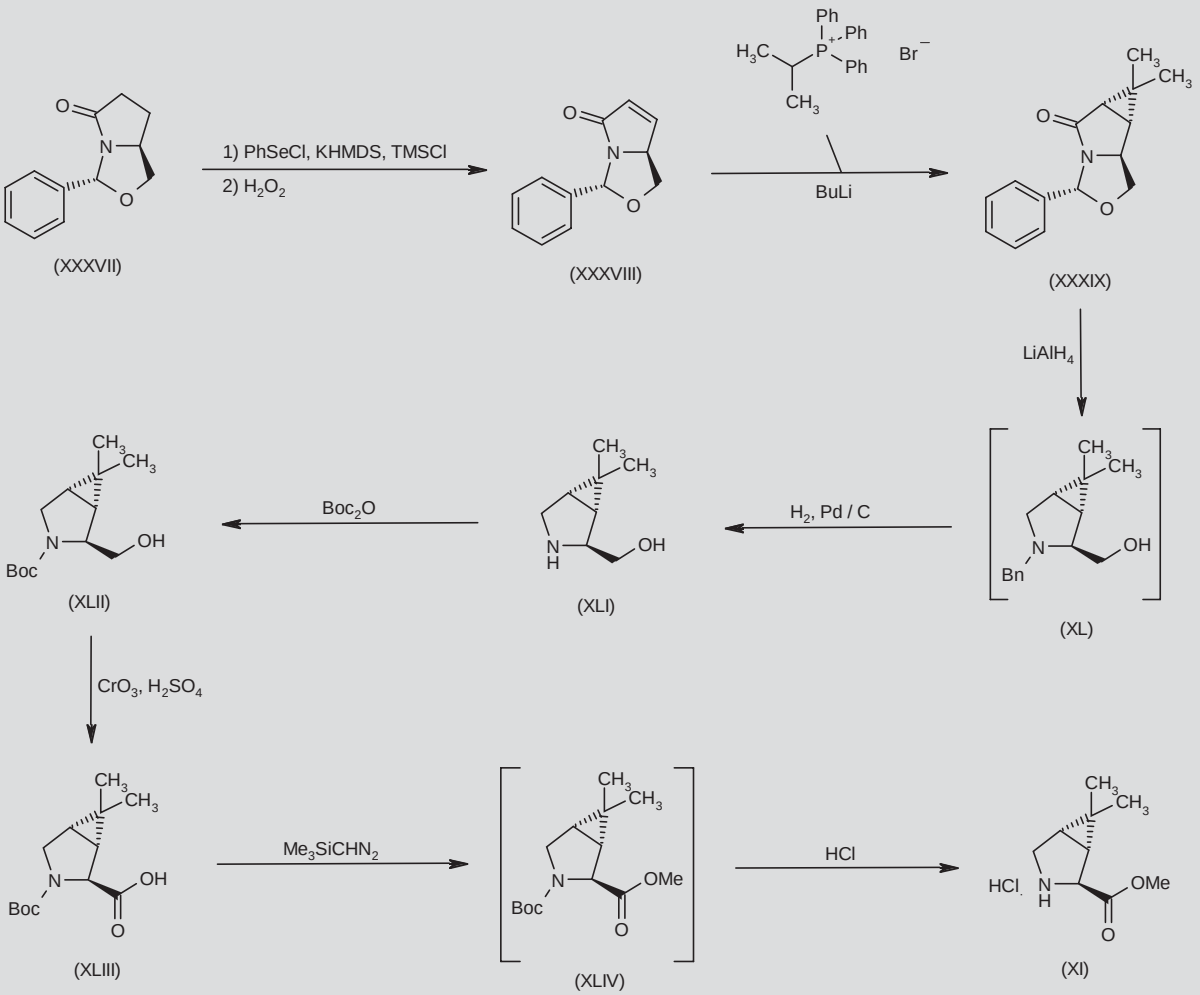
Alternatively, caronic anhydride (XLVI) is reacted with NH_4OH in H_2O at 155 °C or THF at 180 °C to give 6,6-dimethyl-3-azabicyclo[3.1.0]-hexane-2,4-dione (L), which can also be prepared by debenzylation of intermediate (XLVII) with H_2 in the presence of Pd/C or Pt/C. Reduction of imide (L) with $LiAlH_4$ in refluxing THF then yields the bicyclic amine (XLIX). This secondary amine is converted to the corresponding imine (LII) by chlorination with NaClO in methyl *tert*-butyl ether, followed by treatment of the intermediate chloramine (LI) with NaOH in the presence of Bu_4NOH or NBC in MeOH (15), or alternatively by direct oxidation of amine (XLIX) with $K_2S_2O_8$ in the presence of $AgNO_3$ and NaOH in acetonitrile. Addition of sodium bisulfite to the imine (LII) produces the racemic sulfonate (LIII), which upon cyanation with NaCN yields the α-amino nitrile (LIV). After methanolysis of nitrile (LIV) with HCl in MeOH/MTBE, resolution of the racemic amino ester employing di-*p*-toluoyl-D-tartaric acid in MeOH affords intermediate (XI) (12). Scheme 6.

In a further process, the proline analogue (XI) is prepared starting from ethyl chrysanthemate (LV). Oxidative cleavage of the isobutenyl side-chain of compound (LV) with $KMnO_4$ followed by alkaline hydrolysis of the ethyl ester group provides caronic acid (XLV) as a mixture of *cis*- and *trans*-isomers. Diacid (XLV) is then converted to the bicyclic anhydride (XLVI) using either trifluoroacetic anhydride or acetic anhydride as dehydrating reagents. Ring opening of anhydride (XLVI) with allyl alcohol and quinidine, followed by resolution with (*R*)-(+)-α-methylbenzylamine gives the chiral monoallyl ester (LVI), which is subsequently coupled with ammonium bicarbonate by means of di-*tert*-butyl dicarbonate and pyridine to afford the amide ester (LVII). After reduction of compound (LVII) with $LiAlH_4$, the resulting amino alcohol (LVIII) is protected as the benzyl carbamate (LIX) by treatment with benzyl chloroformate and K_2CO_3. The primary alcohol (LIX) is then oxidized to aldehyde (LX) by means of sodium hypochlorite and a catalytic amount of TEMPO. Cyclization of aldehyde (LX) with AcOH in EtOH followed by replacement of the EtOH solvent with THF gives a mixture of the bicyclic hemiaminal (LXI) and its *O*-ethyl derivative (LXII), which, without separation, is treated with cyanotrimethylsilane and boron trifluoride etherate to afford nitrile (LXIII). Addition of NaOMe to the nitrile (LXIII) followed by aqueous hydrolysis of the obtained imidate (LXIV) provides ester (LXV), which can be alternatively obtained by treatment of nitrile (LXIII) with acetyl chloride in MeOH, followed by addition of water. Finally, the benzyl carbamate (LXV) is then deprotected by hydrogenation over Pd/C to yield the cyclopropane-fused prolinate ester (XI) (13). Scheme 7.

BACKGROUND

Hepatitis C virus (HCV) infects around 170 million people worldwide, leading if not treated to a chronic form of hepatitis which causes 10- to 20-year morbidity due to either cirrhosis and hepatic failure or

Scheme 5. Sythesis of Intermediate (XI)

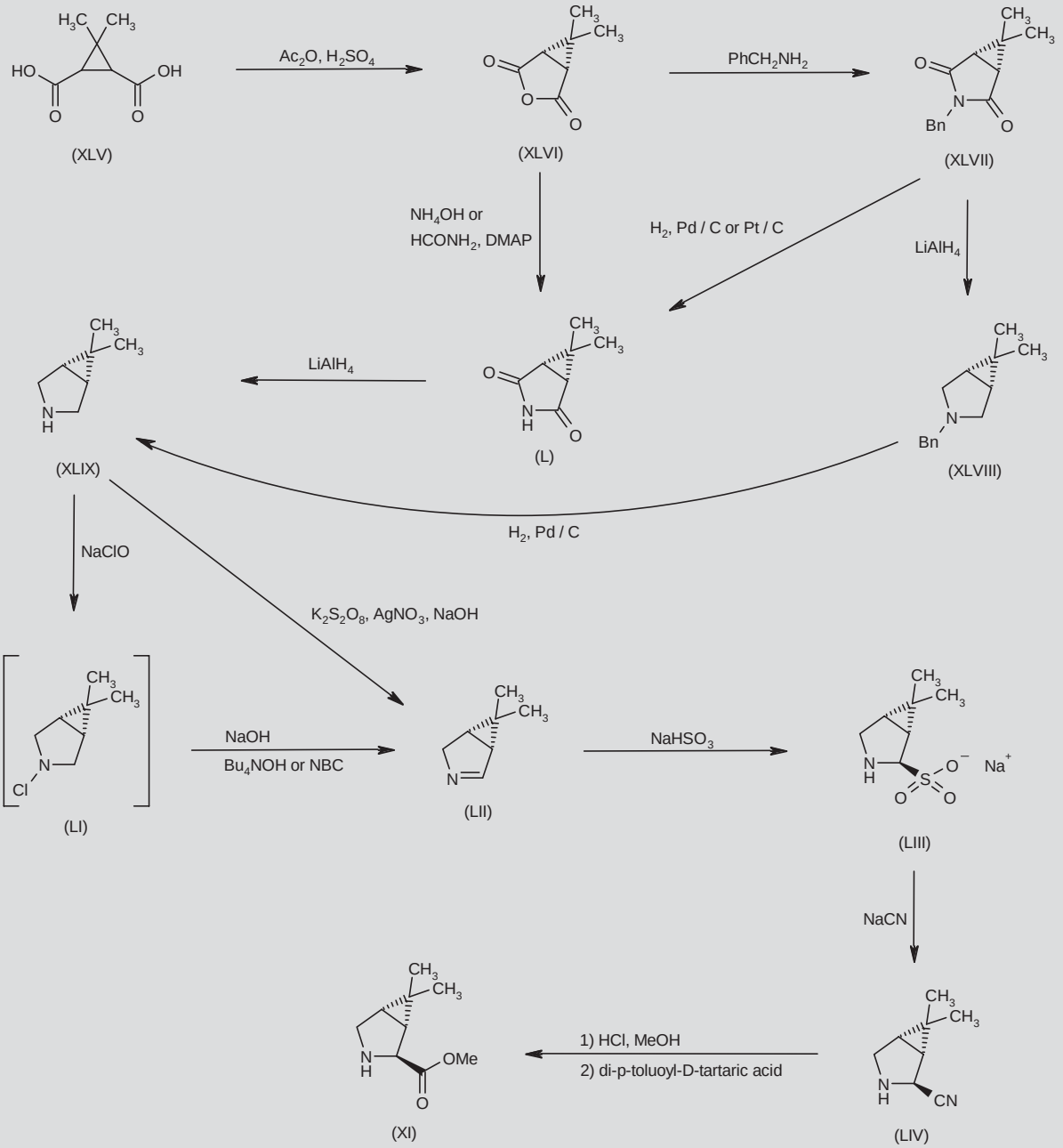


hepatocellular carcinoma (14). The current standard of care for chronic HCV infection is weekly s.c. pegylated interferon alfa (peginterferon) alone or in combination with daily oral ribavirin. The goal of the treatment is to prevent complications of HCV infection through eradication of the virus, and treatment success is defined as undetectable HCV RNA 6 months after the completion of antiviral therapy (sustained virological response) (15). Although the combination peginterferon/ribavirin achieves sustained virological response in 70% of the patients with the majority of HCV genotypes, this response is only 40% for genotype 1, the major genotype affecting North America, Europe and Japan (15, 16). Lack of a complete response, relapse following therapy and premature termination of therapy due to lack of tolerability and side effects contribute to the poor eradication rate observed among genotype 1-infected patients (15). Therefore, new treatment strategies are being developed, including the optimization of current regimens, the use of additional agents with novel mechanisms of action and antifibrotic strategies (17).

HCV is an enveloped, positive-strand RNA virus. Once it has entered in a suitable host cell its genome serves as a template for translation to a 3,000-amino-acid polyprotein that undergoes proteolytic maturation by host- and virus-encoded proteases. The virus-encoded protease responsible for processing the nonstructural portion of the polyprotein is named NS3 and forms a heterodimeric complex with the NS4A protein, an essential cofactor that enhances its enzymatic activity (18). In addition to its role in processing the NS region of the HCV polyprotein, NS3 acts directly against host cells, abrogating the interferon response (19, 20).

Boceprevir (SCH-503034) is a potent, orally bioavailable HCV NS3 protease inhibitor in phase III clinical trials for the treatment of chronic HCV genotype 1 infection in combination with peginterferon with or without added ribavirin. In 2008 the compound received fast track designation from the FDA for the treatment of chronic HCV genotype 1 virus infection in these resistant patients.

Scheme 6. Alternative Synthesis of Intermediate (XI)

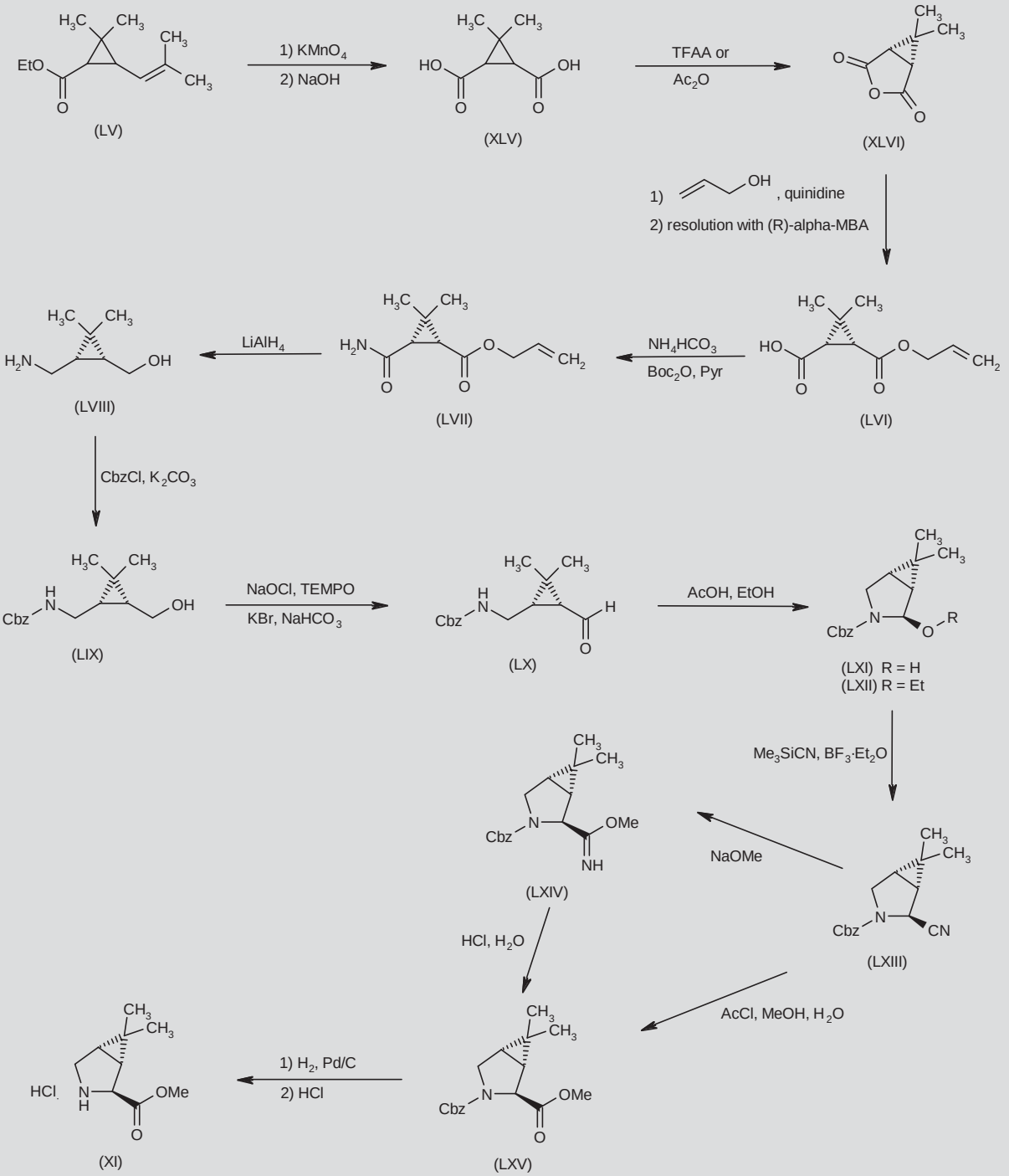


Boceprevir was generated by modification of a ketoamide undecapeptide synthesized by using structure-assisted design to trap the catalytic serine (S139) of the HCV NS3 protease. The undecapeptide showed excellent inhibition of the protease and systematic truncations and modifications of amino acid residues led to the discovery of the potent low-molecular-weight inhibitor boceprevir (4). Boceprevir forms a covalent adduct between the active-site serine and the carbonyl carbon of the ketoamide. Crystallographic analysis showed that it also binds to the active site of the protease in a manner analogous to the substrate (4, 16, 21).

PRECLINICAL PHARMACOLOGY

Boceprevir inhibited NS3 protease activity in cell-free enzyme assays in a time-dependent and concentration-related manner, with an overall inhibition constant (K_i) of 14 nM. The compound also showed potent inhibition of NS3 in the HCV replicon system in vitro, as monitored by immunofluorescence and real-time PCR analysis. Continuous exposure of replicon-bearing cell lines to 6 times the 90% effective concentration of boceprevir for 15 days resulted in a > 4 log reduction in replicon RNA. These studies also

Scheme 7. Alternative Synthesis of Intermediate (XI)



showed that combination of boceprevir with interferon was more effective in suppressing replicon synthesis than either compound alone (16).

NS3 protease-resistant mutations have been identified by culturing replicon cells in the presence of inhibitors. Structural analysis identified atomic interactions that allowed each mutant enzyme to be resistant to one or more inhibitors. The A156T mutation is a major determinant of resistance to boceprevir and other NS3 protease inhibitors, and increased the boceprevir K_i by 400-fold. In contrast, D168V and D168Q mutations did not affect boceprevir activity (22).

The combination of boceprevir with the HCV polymerase inhibitors valopicitabine (NM-283) and HCV-796 has been investigated in vitro (23-25). Combination with the HCV NS5B polymerase inhibitor valopicitabine was investigated using its active metabolite, NM-107 (23). These studies showed that the combination of compounds targeting different HCV enzymes caused a concentration-dependent enhancement of replicon inhibition compared with each inhibitor alone, with no additive cytotoxicity observed. Replicon studies demonstrated that genetic variants exhibiting reduced susceptibility can be selected from each compound. No cross-resistance was found between boceprevir and the polymerase inhibitors and the combination significantly reduced the frequency of the emergence of resistant colonies compared to each inhibitor used alone (23-25).

PHARMACOKINETICS AND METABOLISM

Boceprevir was rapidly absorbed following oral administration, with a mean t_{max} of 1-2.25 h across doses (50-800 mg) and a dose-related C_{max} and AUC, achieving plasma concentrations in the range of the IC_{90} derived from HCV replicon assays (26, 27). After attaining t_{max}, plasma levels of boceprevir declined in a biphasic manner, with a mean terminal half life of 7-15 h (27).

A single-dose study in patients with varying degrees of liver impairment demonstrated that liver impairment slightly increases AUC and C_{max} (with prolonged t_{max}) of boceprevir, without significant differences in any pharmacokinetic parameter when compared to healthy individuals (28).

Ritonavir, an anti-HIV agent that potently inhibits cytochrome P450 3A, strongly inhibited boceprevir metabolism in rat and human microsomes in vitro. Upon coadministration of boceprevir with ritonavir in rats, plasma exposure of the HCV inhibitor was increased by more than 15-fold, and plasma concentrations 8 h after dosing were increased by more than 50-fold. The doses of ritonavir required for pharmacokinetic boosting of boceprevir are well tolerated in HCV/HIV-coinfected individuals, suggesting a potential clinical application in these patients (29).

SAFETY

Phase I clinical studies showed that boceprevir is well tolerated at doses up to 400 and 800 mg/day, with adverse effects similar to the placebo groups (26, 30). Moreover, a single-dose study showed that boceprevir was well tolerated in patients with varying degrees of stable chronic liver impairment (28).

A clinical study in null responders to peginterferon/ribavirin showed that the safety profile of the combination peginterferon/ribavirin with boceprevir (800 mg/day) was similar to that seen with peginterferon/ribavirin, except for incremental anemia and nausea. The occurrence of skin disorders, including rash, did not increase (31).

The HCV SPRING-1 study performed in previously untreated genotype 1 patients to evaluate boceprevir (800 mg/day) used three treatment regimens for the combination: 1) 4 weeks of peginterferon plus ribavirin (800-1400 mg/day) followed by addition of boceprevir to the combination for 24 or 44 weeks; 2) boceprevir in combination with peginterferon and high-dose ribavirin (800-1400 mg/day) for 28 or 48 weeks; and 3) boceprevir in combination with peginterferon and low-dose ribavirin (400-1000 mg/day) for 48 weeks. The most common adverse events reported in the boceprevir arms were fatigue, anemia, nausea and headache. The incidence of rash-related adverse events was similar for boceprevir-containing regimens and the peginterferon/ribavirin control. Treatment discontinuations due to adverse events were between 9% and 19% for patients in boceprevir arms compared to 8% in the control arm (32).

CLINICAL STUDIES

Boceprevir plus peginterferon demonstrated potent antiviral activity in HCV genotype 1-infected patients who were nonresponders to peginterferon alone (30). A clinical study in null responders to peginterferon/ribavirin showed that some nonresponders can achieve sustained virological response with peginterferon/ribavirin plus 800 mg boceprevir, although outcome was dependent on residual response to interferon. Initial therapy with peginterferon/ribavirin prior to addition of boceprevir provided additional benefit. The same study showed that lower doses of boceprevir were less effective (31, 33).

The SPRINT-1 study was performed in 595 previously untreated HCV genotype 1-infected patients to compare several regimens of boceprevir combined with peginterferon alfa-2b and ribavirin. Peginterferon (1.5 µg/kg weekly) and low or high doses of ribavirin were combined with boceprevir 800 mg t.i.d. for 28 or 48 weeks. Boceprevir substantially improved sustained virological response with 28 weeks of therapy and nearly doubled the virological response compared to the current peginterferon/ribavirin standard of care (48 weeks). Use of a 4-week lead-in with peginterferon and ribavirin prior to the addition of boceprevir reduced the incidence of viral breakthrough and substantially increased sustained virological response (32, 34, 35).

The selection of resistant variants of HCV during treatment with boceprevir has been described (36). The long-term persistence of NS3 resistance mutations was investigated in six patients from phase Ib studies who received either boceprevir alone (up to 400 mg/day) or combination therapy with peginterferon. Clonal sequence analysis revealed different resistant variants of the protease in four of the six patients. None of these patients received further antiviral therapy after boceprevir. High frequencies of resistant variants were detected in two patients after 1-year follow-up (37).

Boceprevir is currently in phase III clinical trials for the treatment of chronic HCV genotype 1 in combination with peginterferon alfa-2b and ribavirin in patients who demonstrate interferon responsiveness but who failed to achieve sustained virological response on prior treatment with any combination therapy of peginterferon alfa and ribavirin (38), as well as in previously untreated patients (39).

SOURCE

Schering-Plough (US).

REFERENCES

1. Njoroge, F.G., Venkatraman, S. (Schering Corp.). *An inhibitor of heptatitis C*. US 2005249702, WO 2005107745.

2. Saksena, A., Nair, L.G., Lovey, R.G. et al. (Schering Corp.; Dendreon Corp.). *Novel peptides as NS3-serine protease inhibitors of hepatitis C virus.* CA 2473032, EP 1481000, JP 2005524628, US 2007032433, US 7244721, WO 2003062265.
3. Lovey, R.G., Tamura, S.Y., Bennett, F. (Dendreon Corp.; Schering Corp.). *Novel peptides as NS3-serine protease inhibitors of hepatitis C virus.* CA 2410662, EP 1385870, JP 2004504404, JP 2009051860, US 2003216325, US 2004254117, US 7012066, WO 2002008244.
4. Venkatraman, S., Bogen, S.L., Arasappan, A. et al. *Discovery of (1R,5S)-N-[3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl] amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S) carboxamide (SCH 503034), a selective, potent, orally bioavailable hepatitis C virus NS3 protease inhibitor: A potential therapeutic agent for the treatment of hepatitis C infection.* J Med Chem 2006, 49(20): 6074-86.
5. Wu, G.G., Xie, J., Rashatasakhon, P. (Schering Corp.). *An oxidation process for the preparation of N-[3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[N-[(tert-butylamino)carbonyl]-3-methyl-L-valyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide and related compounds.* CA 2628738, EP 1966233, JP 2009515894, US 2007149459, US 7528263, WO 2008010831.
6. Wong, G.S.K., Lee, H.-C., Vance, J.A., Tong, W., Iwama, T. (Schering Corp.). *Process for preparing (1R,2S,5S)-N-[(1S)-3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[(2S)-2-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide.* CA 2672620, WO 2008079216.
7. Sudhakar, A., Dahanukar, V., Zavialov, I.A. et al. (Schering Corp.). *Process and intermediates for the preparation of (1R,2S,5S)-3-azabicyclo-[3,1,0]hexane-2-carboxamide, N-[3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[(2S)-2-[[[1,1-dimethylethyl]amino]carbonylamino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl.* CA 2526629, EP 1641754, JP 2006528133, US 2005059800, US 7326795, WO 2004113294.
8. Dener, J.M. (Virobay, Inc.). *Process for the preparation of (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid.* WO 2009039361.
9. Park, J., Vater, E.J., Dong, S., Iwama, T., Raghavan, R.R., Lee, H.-C., Wong, G.S.K. (Schering Corp.). *Preparation of 3-amino-3-(cyclobutylmethyl)-2-(hydroxy)-propionamide hydrochloride.* CA 2672570, WO 2008082486.
10. Zhang, R., Mamai, A., Madalengoitia, J.S. *Cyclopropanation reactions of pyroglutamic acid-derived synthons with alkylidene transfer reagents*. J Org Chem 1999, 64(2): 547-55.
11. Kwok, D.-L., Lee, H.-C., Zavialov, I.A. (Schering Corp.). *Dehydrohalogenation process for the preparation of intermediates useful in providing 6,6-dimethyl-3-azabicyclo-[3.1.0]-hexane compounds.* WO 2009073380.
12. Berranger, T., Demonchaux, P. (Schering Corp.*). Process for the preparation of 6,6-dimethyl-3-azabicyclo-[3.1.0]-hexane compounds utilizing bisulfite intermediate.* WO 2008082508.
13. Park, J., Sudhakar, A., Wong, G.S. (Schering Corp.). *Process and intermediates for the preparation of (1R,2S,5S)-6,6-dimethyl-3-azabicyclo-[3,1,0]hexane-2-carboxylates or salts thereof.* JP 2007520434, US 2005059648, WO 2004113295.
14. Alter, H.J., Seeff, L.B. *Recovery, persistence, and sequelae in hepatitis C virus infection: A perspective on long-term outcome*. Semin Liver Dis 2000, 20(1): 17-35.
15. Smith, J.P. *Treatment options for patients with hepatitis C: Role of pharmacists in optimizing treatment response and managing adverse events.* Pharmacotherapy 2008, 28(9): 1151-61.
16. Malcolm, B.A., Liu, R., Lahser, F. et al. *SCH 503034, a mechanism-based inhibitor of hepatitis C virus NS3 protease, suppresses polyprotein maturation and enhances the antiviral activity of alpha interferon in replicon cells*. Antimicrob Agents Chemother 2006, 50(3): 1013-20.
17. Stauber, R.E., Stadlbauer, V. *Novel approaches for therapy of chronic hepatitis C.* J Clin Virol 2006, 36(2): 87-94.
18. Reed, K.E., Rice, C.M. *Overview of hepatitis C virus genome structure, polyprotein processing, and protein properties*. Curr Top Microbiol Immunol 2000, 242: 55-84.
19. Foy, E., Li, K., Wang, C., Sumpter, R. Jr., Ikeda, M., Lemon, S.M., Gale, M. Jr. *Regulation of interferon regulatory factor-3 by the hepatitis C virus serine protease*. Science 2003, 300(5622): 1145-8.
20. Foy, E., Li. K., Sumpter, R. Jr. et al. *Control of antiviral defenses through hepatitis C virus disruption of retinoic acid-inducible gene-I signaling*. Proc Natl Acad Sci U S A 2005, 102(8): 2986-91.
21. Prongay, A.J., Guo, Z., Yao, N. et al. *Discovery of the HCV NS3/4A protease inhibitor (1R,5S)-N-[3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino] carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3azabicyclo[3.1.0] hexan-2(S)-carboxamide (Sch 503034) II. Key steps in structure-based optimization.* J Med Chem 2007, 50(10): 2310-8.
22. Guo, Z., Prongay, A., Tong, X. et al. *Computational study of the effects of mutations A156T, D168V, and D168Q on the binding of HCV protease inhibitors*. J Chem Theory Comput 2006, 2: 1657-63.
23. Standring, D.N., Bichko, V., Chase, C. et al. *HCV polymerase (NM107) and protease (boceprevir) inhibitors in combination show enhanced activity and suppression of resistance in the replicon system.* 58th Annu Meet Am Assoc Study Liver Dis (Nov 2-6, Boston) 2007, Abst 1391.
24. Ralston, R., Howe, A.Y., Chase, R. et al. *Favorable cross-resistance profile of HCV-796 and Sch-503034 and enhanced anti-replicon activity mediated by combination treatment.* Gastroenterology [Dig Dis Week (May 19-24, Washington, D.C.) 2007] 2007, 132(4, Suppl. 2): Abst 364.
25. Howe, A.Y., Ralston, R., Chase, R. et al. *Favorable cross-resistance profile of two novel hepatitis C virus inhibitors, SCH-503034 and HCV-796, and enhanced anti-replicon activity mediated by the combined use of both compounds*. 42nd Annu Meet Eur Assoc Study Liver (EASL) (April 11-15, Barcelona) 2007, Abst 432.
26. Zeuzem, S., Sarrazin, C., Rouzier, R. et al. *Anti-viral activity of SCH503034, a HCV protease inhibitor, administered as monotherapy in hepatitis C genotype-1 (HCV-1) patients refractory to pegylated interferon (PEG-INF-α).* 56th Annu Meet Am Assoc Study Liver Dis (Nov 11-15, San Francisco) 2005, Abst 94.
27. Zhang, J., Gupta, S., Rouzier, R., Calzetta, A., Cutler, D.L. *Single dose pharmacokinetics of a novel hepatitis C protease inhibitor, SCH503034, in an oral capsule formulation*. 56th Annu Meet Am Assoc Study Liver Dis (Nov 11-15, San Francisco) 2005, Abst 862.
28. Preston, R.A., Alonso, A.B., Feely, W. et al. *SCH503034, an oral HCV protease inhibitor, is well-tolerated in patients with varying degrees of hepatic impairment.* 42nd Annu Meet Eur Assoc Study Liver (EASL) (April 11-15, Barcelona) 2007, Abst 545.
29. Kempf, D.J., Klein, C., Chen, H.J. et al. *Pharmacokinetic enhancement of the hepatitis C virus protease inhibitors VX-950 and SCH 503034 by co-dosing with ritonavir*. Antivir Chem Chemother 2007, 18(3): 163-7.
30. Sarrazin, C., Rouzier, R., Wagner, F. et al. *SCH 503034, a novel hepatitis C virus protease inhibitor, plus pegylated interferon alpha-2b for genotype 1 nonresponders.* Gastroenterology 2007, 132(4): 1270-8.
31. Schiff, E., Poordad, F., Jacobson, I. et al. *Role of interferon response during re-treatment of null responders with boceprevir combination therapy: Results of phase II trial.* Gastroenterology [Dig Dis Week (May 17-22, San Diego) 2008] 2008, 134(4, Suppl. 1): Abst 162.
32. Kwo, P., Lawitz, E., McCone, J. et al. *HCV SPRINT-1: Boceprevir plus peginterferon alfa-2b/ribavirin for the treatment of genotype 1 chronic hepatitis C in previously untreated patients*. Hepatology [Liver Meet (Oct 31-Nov 4, San Francisco) 2008] 2008, 48(4, Suppl.): Abst LB16.

33. Schiff, E., Poordad, F., Jacobson, I. et al. *Boceprevir (B) combination therapy in null responders (NR): Response dependent of interferon responsiveness.* 43rd Annu Meet Eur Assoc Study Liver (EASL) (April 23-27, Milan) 2008, Abst.

34. Kwo, P., Lawitz, E., McCone, J. et al. *HCV SPRINT-1: Boceprevir plus peginterferon alfa-2b/ribavirin for treatment of genotype 1 chronic hepatitis C in previously untreated patients.* 13th Int Symp Viral Hepatitis Liver Dis (March 20-24, Washington) 2009, Abst OP-121.

35. Kwo, P., Lawitz, E., McCone, J. et al. *HCV SPRINT-1 final results2: SVR 24 from a Phase 2 study of boceprevir plus Pegintron™ (peginterferon alfa-2B)/ribavirin in treatment naïve subjects with genotype-1 with genotype-1 chronic hepatitis C.* 44th Annu Meet Eur Assoc Study Liver (EASL) (April 22-26, Copenhagen) 2009, Abst.

36. Susser, S., Welker, M.W., Zettler, M. et al. *Clonal analysis of mutations selected in the HCV NS3 protease domain of genotype 1 non-responders treated with boceprevir (SCH503034).* 43rd Annu Meet Eur Assoc Study Liver (EASL) (April 23-27, Milan) 2008, Abst.

37. Susser, S., Forestier, N., Welker, M.W., Vermehren, J., Karey, U., Zeuzem, S., Sarrazin, C. *Detection of resistant variants in the hepatitis C virus NS3 protease gene by clonal sequencing at long-term follow-up in patients treated with boceprevir.* 44th Annu Meet Eur Assoc Study Liver (EASL) (April 22-26, Copenhagen) 2009, Abst.

38. *Boceprevir in subjects with chronic hepatitis C genotype 1 who failed prior treatment with peginterferon/ribavirin (Study P05101AM1) (NCT00708500).* ClinicalTrials.gov Web site, August 28, 2009.

39. *Safety and efficacy of boceprevir in previously untreated subjects with chronic hepatitis C genotype 1 (Study P05216AM1) (SPRINT-2) (NCT00705432).* ClinicalTrials.gov Web site, August 28, 2009.