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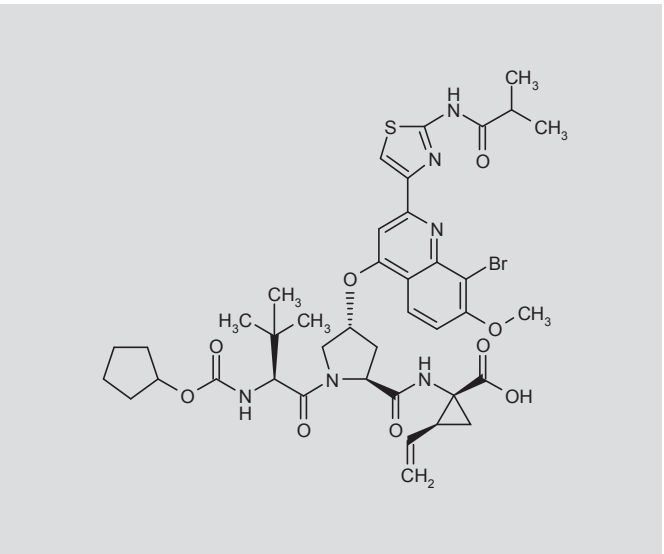
BI-201335

Treatment of Hepatitis C Virus
Serine Protease NS3/Non-Structural Protein 4A (NS4A) Inhibitor

N-(Cyclopentyloxycarbonyl)-3-methyl-L-valyl-4(*R*)-[8-bromo-2-[2-(isobutyrylamino)thiazol-4-yl]-7-methoxyquinolin-4-yloxy]-*N*-[1(*R*)-carboxy-2(*S*)-vinylcyclopropyl]-L-prolinamide

InChI: 1S/C40H49BrN6O9S/c1-8-21-17-40(21,36(51)52)46-34(49)27-15-23(18-47(27)35(50)32(39(4,5)6)44-38(53)56-22-11-9-10-12-22)55-29-16-25(26-19-57-37(43-26)45-33(48)20(2)3)42-31-24(29)13-14-28(54-7)30(31)41/h8,13-14,16,19-23,27,32H,1,9-12,15,17-18H2,2-7H3,(H,44,53)(H,46,49)(H,51,52)(H,43,45,48)/t21-,23-,27?,32-,40-/m1/s1



$C_{40}H_{49}BrN_6O_9S$
Mol wt: 869.821
EN: 644871

SUMMARY

Chronic hepatitis C affects an estimated 170 million people worldwide and is the leading indication for liver transplantation in the U.S. Until recently, eradication of chronic hepatitis C depended on the combination of pegylated interferon (pegIFN) and ribavirin (RBV). This combination is effective in only 40-50% of patients infected with hepatitis C virus (HCV) genotype 1, and 30-40% of patients co-infected with HIV. It also carries a high burden of side effects, mostly flu-like illness, fatigue, depression and anemia. This low-efficacy/high-toxicity regimen has motivated the search for a more potent treatment with an improved side effect profile. In this context, various therapeutic agents targeting viral enzymes critical to HCV replication have been identified. BI-201335 is a potent and selective HCV serine protease NS3/non-structural protein 4A (NS4A) inhibitor that recently entered phase III clinical trials. In phase II trials, cure rates above 80% were reported for previously untreated patients, with the majority being eligible for shorter treatment duration. Its high potency, once-daily dosing and good safety profile suggest it could be included in future interferon-free direct-acting antiviral combinations.

Key words: Hepatitis C virus – NS3/NS4A inhibitor – Protease inhibitor – BI-201335

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SYNTHESIS*

BI-201335 can be synthesized by the following methods:

Cyclization of the α-bromoketone (I) with *N*-isobutyrylthiourea (II) in *i*-PrOH at 75 °C produces the thiazole derivative (III), which upon methyl ester hydrolysis using LiOH in H_2O/MeOH/THF gives directly BI-201335 (1, *2*). Scheme 1.

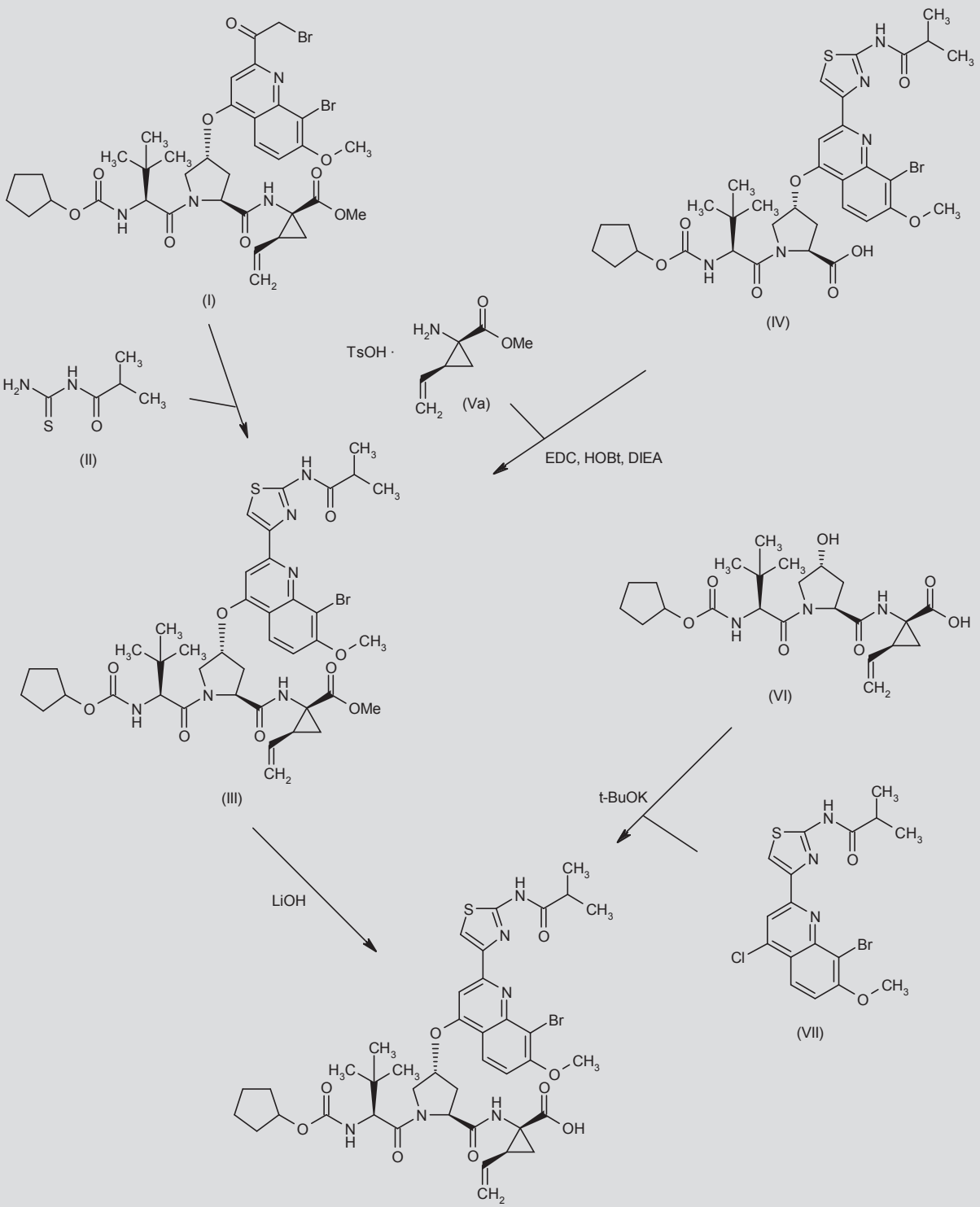
In an alternative method, the methyl ester precursor (III) is obtained by condensation of the dipeptide derivative (IV) with methyl 1(*R*)-amino-2(*S*)-vinylcyclopropanecarboxylate tosylate salt (Va) by means of EDC, HOBt and DIEA in DMF (*2*). Scheme 1.

In a different strategy, the tripeptide carbamate (VI) is coupled with the chloroquinoline derivative (VII) by means of *t*-BuOK in DMSO to afford BI-201335 (*2*). Scheme 1.

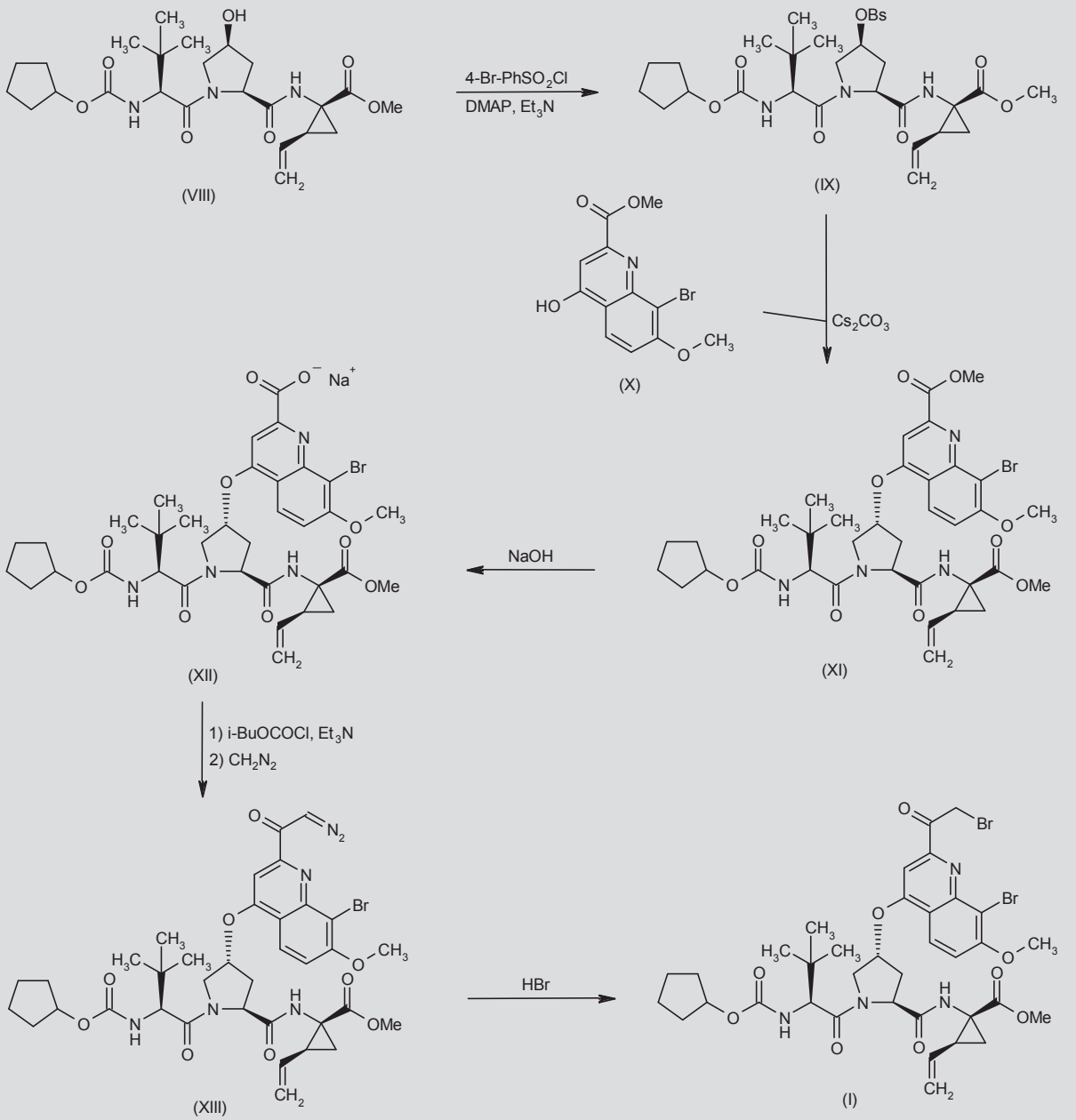
The bromoketone intermediate (I) is prepared as follows:

Alcohol (VIII) is converted to the corresponding brosylate (IX) by treatment with *p*-bromobenzenesulfonyl chloride in the presence of DMAP and Et_3N in CH_2Cl_2 (1, 3, 4). Subsequent displacement of the sulfonate group of compound (IX) with the quinolinol (X) in the presence of Cs_2CO_3 in NMP affords the ether adduct (XI) (1, 3). Selective hydrolysis of diester (XI) by means of NaOH in THF/H_2O generates the sodium salt (XII), which, after conversion to a mixed anhydride with *i*-BuOCOCl and Et_3N in THF, is treated in situ with CH_2N_2 to give the diazoketone (XIII). Finally, reaction of diazoketone (XIII) with concentrated HBr in THF yields the α-bromoketone (I) (1, 3). Scheme 2.

Scheme 1. Synthesis of BI-201335



Scheme 2. Synthesis of Bromoketone Intermediate (I)



Tripeptide derivative (VIII) is obtained by coupling of *N*-Boc-4(*R*)-hydroxy-L-proline (XIV) with methyl 1(*R*)-amino-2(*S*)-vinylcyclopropanecarboxylate (Vb) by means of TBTU and DIEA in DMF to afford amide (XV). Subsequent Mitsunobu condensation of alcohol (XV) with *p*-nitrobenzoic acid (PNBA) in the presence of PPh_3 and DEAD in THF gives the fully protected dipeptide (XVI), from which the *N*-Boc group is removed by treatment with HCl in dioxane, yielding the corresponding amine (XVII) (3, 4). Coupling of dipeptide ester (XVII) with *N*-(cyclopentyloxycarbonyl)-3-methyl-L-valine (XVIII) [prepared by condensation of cyclopentyl succinimidyl carbonate

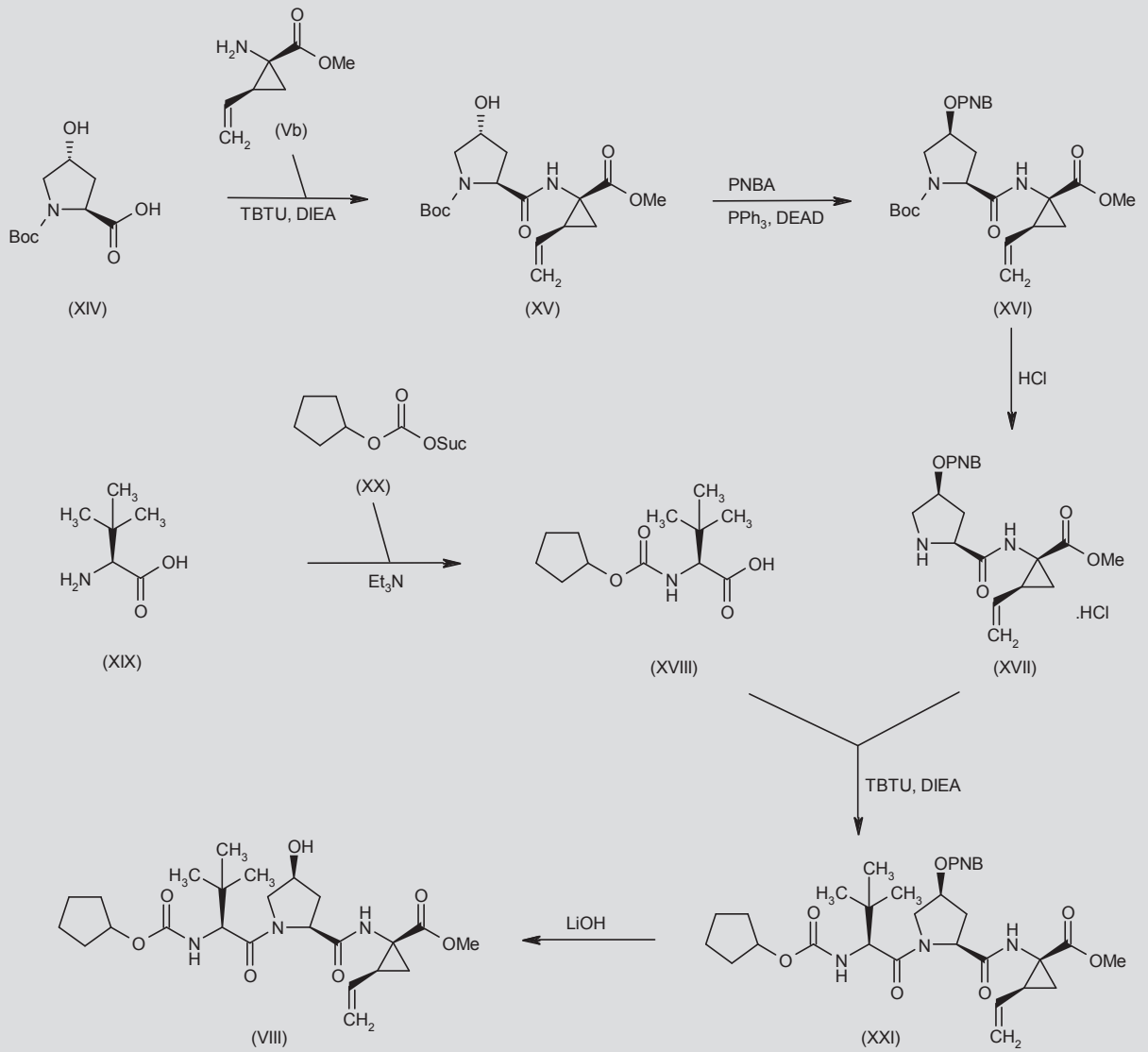
(XX) with 3-methyl-L-valine (XIX) by means of Et_3N in THF/H_2O (1, 4)] in the presence of TBTU and DIEA in CH_2Cl_2 provides tripeptide derivative (XXI), which by selective hydrolysis of the PNB ester (XXI) by means of LiOH in H_2O/THF produces the tripeptide derivative (VIII) (1, 3, 4). Scheme 3.

The peptide building blocks (IV) and (VI) are prepared as follows:

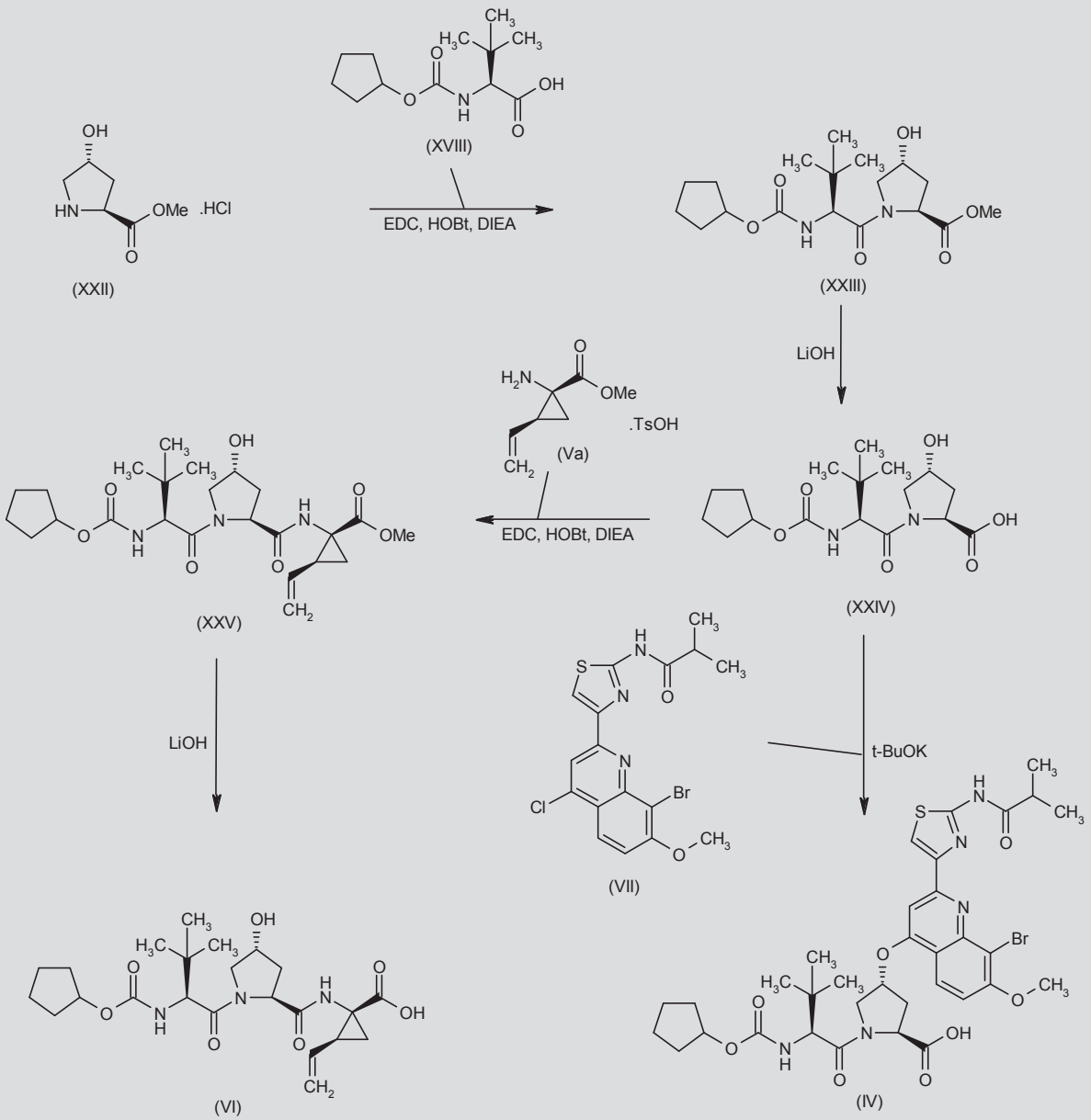
Coupling of 4(*R*)-hydroxy-L-proline methyl ester hydrochloride (XXII) with *N*-(cyclopentyloxycarbonyl)-3-methyl-L-valine (XVIII) by means of EDC, HOBt and DIEA in DMF affords the dipeptide derivative (XXIII), which is then subjected to methyl ester hydrolysis with LiOH in H_2O/MeOH/THF to yield dipeptide carbamate (XXIV) (isolated as solvate with MTBE). Subsequent condensation of compound (XXIV) with the chloroquinoline (VII) using *t*-BuOK in DMSO gives rise to the key intermediate (IV) (2). Scheme 4.

Coupling of the dipeptide carbamate (XXIV) with methyl 1(*R*)-amino-2(*S*)-vinylcyclopropanecarboxylate tosylate salt (Va) by means of EDC, HOBt and DIEA in DMF leads to the tripeptide ester (XXV), which by hydrolysis with LiOH in H_2O/MeOH/THF provides the carboxylic acid intermediate (VI) (2). Scheme 4.

Scheme 3. Synthesis of Tripeptide Derivative (VIII)



Scheme 4. Synthesis of Peptide Building Blocks (IV) and (VI)



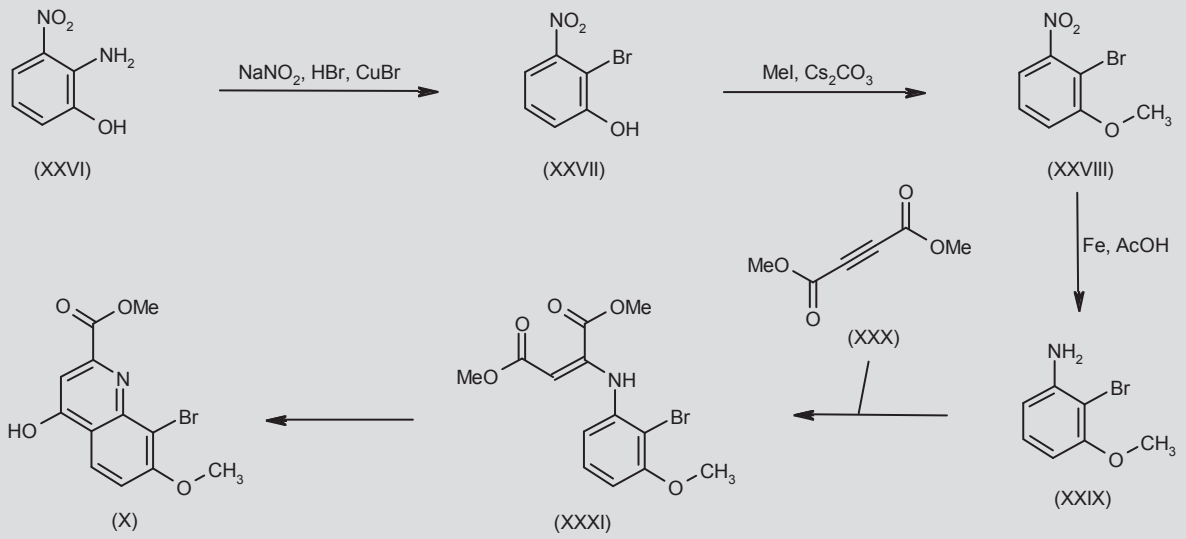
Hydroxyquinoline derivative (X) is obtained as follows:

Sandmeyer reaction of 2-amino-3-nitrophenol (XXVI) using $NaNO_2$ and HBr in the presence of CuBr in H_2O/dioxane gives 2-bromo-3-nitrophenol (XXVII), which by *O*-alkylation with MeI in the presence of Cs_2CO_3 in DMF affords the methyl ether (XXVIII). Subsequent reduction of the nitro derivative (XXVIII) with Fe powder in refluxing AcOH/EtOH provides 2-bromo-3-methoxyaniline (XXIX) (3, 4). Addition of aniline (XXIX) to dimethyl acetylene dicarboxylate (XXX) in refluxing MeOH produces the amino diester (XXXI), which by cyclization at 240 °C in diphenyl ether affords the quinoline (X) (1, 3, 4). Scheme 5.

The thiazolylquinoline intermediate (VII) is prepared by the following method:

ortho-Metalation of *N*-Boc-*m*-anisidine (XXXII) with BuLi in cold THF, followed by bromination with perfluorooctyl bromide, gives

Scheme 5. Synthesis of Hydroxiquinolone Derivative (X)



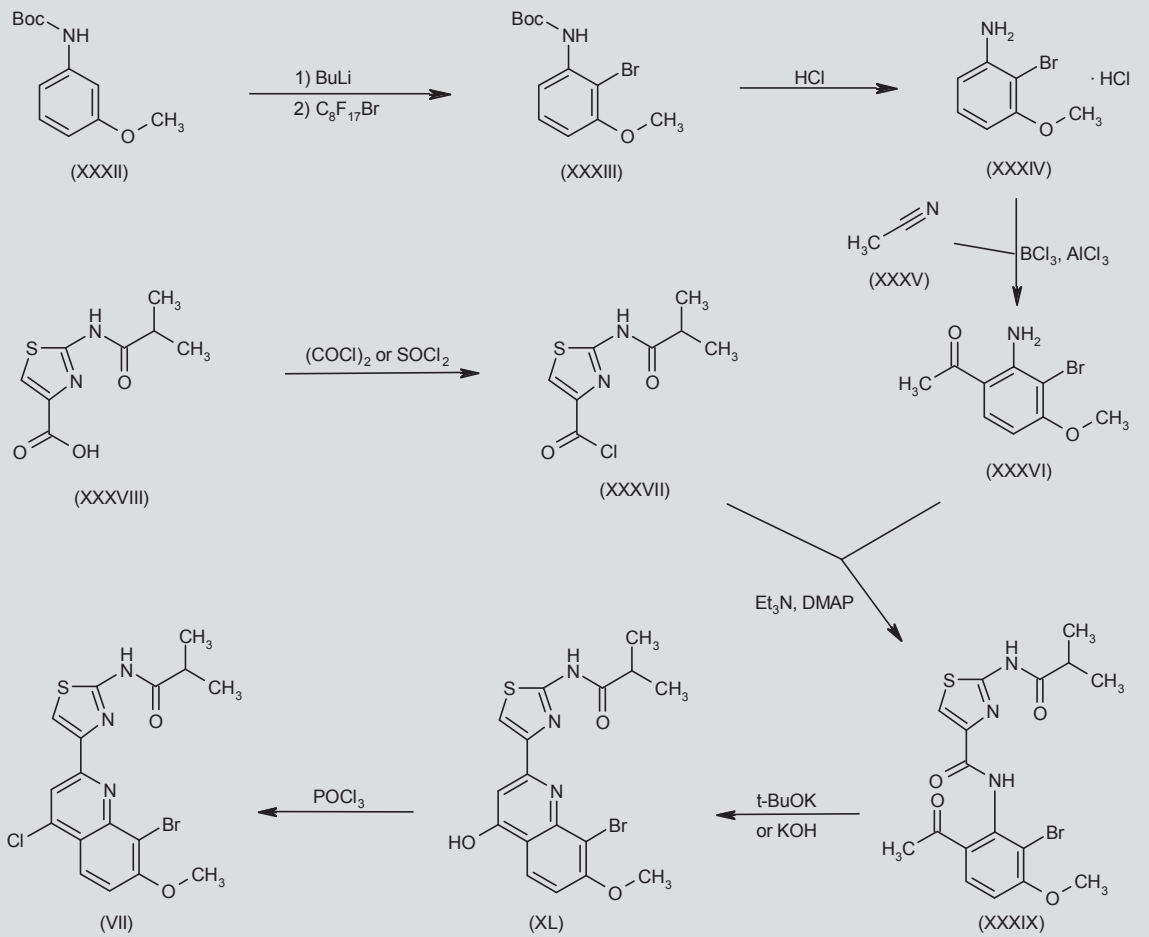
N-Boc-2-bromo-3-methoxyaniline (XXXIII), which by Boc group cleavage with HCl in diglyme at 100 °C provides 2-bromo-3-methoxyaniline hydrochloride (XXXIV). Friedel–Crafts acylation of bromoanisidine (XXXIV) with acetonitrile (XXXV) in the presence of BCl_3 and $AlCl_3$ in chlorobenzene at 100 °C affords 2′-amino-3′-bromo-4′-methoxyacetophenone (XXXVI) (4), which is then coupled with the acid chloride (XXXVII) [prepared by chlorination of 2-isobutyrylaminothiazole-4-carboxylic acid (XXXVIII) with either $(COCl)_2$ in DMF/THF (4, 5) or $SOCl_2$ in NMP (5)] by means of Et_3N and DMAP in THF (2) to provide the corresponding carboxamide (XXXIX) (2, 5). Intramolecular cyclocondensation of the ketoamide (XXXIX) in the presence of either *t*-BuOK in DME at 80-85 °C (2) or KOH in *t*-BuOH (5) yields the quinolinol (XL), which is then chlorinated with $POCl_3$ in dioxane at 75 °C to obtain the 4-chloroquinoline derivative (VII) (2, 5). Scheme 6.

BACKGROUND

Chronic hepatitis C affects an estimated 170 million people worldwide and is the leading indication for liver transplantation in the U.S. (6). Since the beginning of the 21st century, hepatitis C virus (HCV) drug development has been a very active field of clinical research. Until recently, eradication of chronic HCV depended on the combination of pegylated interferon (pegIFN) and ribavirin (RBV), which was approved by the Food and Drug Administration (FDA) in 1998. While this combination is effective in only 40-50% of patients infected with HCV genotype 1 (7), and 30-40% of patients co-infected with HIV (8), it also carries a high burden of side effects, mostly flu-like illness, fatigue, depression and anemia (7). This low-efficacy/high-toxicity regimen has motivated the search for a more potent treatment with an improved side effect profile. The lack of a tissue culture model had been a major obstacle to HCV drug development until recently. Production of infectious HCV in tissue culture is now possible and allows analysis of host–virus interactions (9-11). This was a huge step forward that facilitated anti-HCV drug discovery. Therefore, in the last decade, the HCV pipeline has dramatically grown and various therapeutic agents have been identified that target viral enzymes critical to HCV replication (12, 13).

There are several classes of direct-acting antivirals (DAAs), including the serine protease NS3/non-structural protein 4A (NS4A) inhibitors, the RNA-directed RNA polymerase 5B (NS5B) inhibitors and the non-structural protein 5A (NS5A) inhibitors. NS3/NS4A inhibitors are the farthest ahead in terms of clinical development. The first HCV DAA to have shown clinical proof of principle was BILN-2061, a reversible inhibitor of HCV NS3/NS4A (14, 15). Development of BILN-2061 was stopped following safety studies conducted in rhesus monkeys showing cardiotoxicity, specifically myocardial vacuolation at light microscopy, within 4 weeks of starting daily dosing (16). Boceprevir (SCH-503034) and telaprevir (VX-950), two linear α-ketoamide derivatives, have successfully gone through phases I to III of clinical development and were approved by the FDA in May 2011 to be used in combination with pegIFN and RBV (17). The combination of one of these protease inhibitors with pegIFN/RBV nearly doubles the chance of cure and allows for shorter treatment duration in the majority of patients (18-21). Although highly effective, this triple combination leads to increased side effects, mostly anemia and dysgeusia with boceprevir and skin reactions and anorectal dis-

Scheme 6. Synthesis of Thiazolylquinoline Intermediate (VII)



comfort with telaprevir. These two protease inhibitors, which have to be taken three times daily, are classified as first-generation, first-wave protease inhibitors. The second-generation protease inhibitors feature linear and macrocyclic noncovalent inhibitors of HCV NS3/NS4A. These second-wave protease inhibitors offer the advantages of convenience, being administered once or twice daily, and improved side effect profiles. Broader genotypic coverage and improved resistance profiles are true characteristics of the second-generation protease inhibitors (22).

BI-201335 is a linear tripeptide carboxylic acid inhibitor of the NS3/NS4A proteases that noncovalently interacts with the enzymes, resulting in high binding affinity. Its carboxylic acid at the *C*-terminus allows for selective interaction with the HCV NS3 protease active site, contributing to its potency (11, 23, 24). The combination of the carboxylic acid at the *C*-terminus and a bromo-quinoline substitution on its proline residue is responsible for its high potency (1). BI-201335 has shown favorable results in preclinical and early clinical phases of development (25-28). It is a potent protease inhibitor administered once daily that appears to have an improved side effect profile compared to the two α-ketoamide derivatives boceprevir and telaprevir.

PRECLINICAL PHARMACOLOGY

A detailed preclinical characterization of BI-201335 has been published (25). In biochemical assays, the median 50% inhibitory concentration (IC_{50}) was determined and converted to apparent K_i values (binding affinity for inhibition) to allow direct comparison of binding affinity across HCV genotypes. BI-201335 showed the great-

est inhibitory potency against HCV genotypes 1a, 1b and 4a (K_{iapp} ± standard deviation [SD] = 1.2 ± 0.2, 2.8 ± 0.5 and 1.8 ± 0.5 nM, respectively). It also inhibits the NS3/NS4A proteases of HCV genotypes 5a and 6a (K_{iapp} ± SD = 5.8 ± 1.0 and 6.1 ± 0.9 nM, respectively). Its inhibitory potency is weaker for HCV genotypes 2a, 2b and 3a (20-, 50- and 190-fold, respectively, vs. genotype 1a). When compared with telaprevir and boceprevir, BI-201335 had similar inhibitory potency against HCV genotypes 1a and 1b. BI-201335 had no activity against the human serine and cysteine proteases elastase and cathepsin B, and little or no activity against 39 proteases tested, which is consistent with its NS3-selective property conferred by the *C*-terminal carboxylic acid (24).

Similar to enzymatic assays, in replicon assays, BI-201335 had low-nanomolar activity against HCV genotypes 1a and 1b. The 50% effective concentrations (EC_{50}) ± SD of BI-201335 against HCV genotypes 1a and 1b in replicon assays were 6.5 ± 0.9 and 3.1 ± 1.2 nM, respectively. For comparison, in that experiment, telaprevir and boceprevir EC_{50} values against genotype 1a were 108- and 85-fold those of BI 201335, respectively, and 174- and 168-fold those for genotype 1b, respectively, despite their excellent enzymatic activity (25). When BI-201335 was combined with either interferon alfa or RBV in replicon assays, additive effects were observed.

PHARMACOKINETICS AND METABOLISM

In animal studies, a good absorption, distribution, metabolism and excretion (ADME) profile was seen. After a single oral administration of BI-201335 at a dose of 5 mg/kg in rats, monkeys and dogs, the drug was rapidly absorbed, as demonstrated by a time to maximum concentration of drug in serum (t_{max}) value of 1-2 hours (25). The oral maximum concentration of drug in serum (C_{max}) ± standard error (SE) was lowest in rats (0.41 µM), intermediate in monkeys (2.0 ± 0.3 µM) and highest in dogs (3.8 ± 0.3 µM). The area under the curve (AUC) ± SE also increased from 1.55 µM·h in rats to 8.3 ± 0.9 µM·h in monkeys and 13 ± 3 µM·h in dogs. In rats, drug levels were higher in liver than plasma, with a mean liver to plasma ratio of 42 in 1 hour. The same favorable distribution was not reported in dogs and monkeys.

In humans, the pharmacokinetics of BI-201335 have been studied in both HCV treatment-naive and treatment-experienced patients in a randomized, placebo-controlled, successive cohort study (26). Treatment-naive patients received BI-201335 monotherapy for 14 days (20, 48, 120 and 240 mg once daily) or matching placebo followed by combination with pegIFN/RBV through day 28. Treatment-experienced patients received BI-201335 at a dose of 48, 120 or 240 mg once daily in combination with pegIFN/RBV for 28 days. The mean t_{max} ranged from 2.0 to 5.57 hours. C_{max}, minimal concentration of drug in serum (C_{min}) and $AUC_{0-\delta}$ increased supraproportionally with the BI-201335 dose. The mean elimination half-life ($t_{1/2}$) was approximately 20-30 hours, with the lowest value being 17.8 hours and the highest value 38.7 hours. This suggested that once-daily dosing was appropriate. No difference was seen between treatment-naive and -experienced patients, although there was significant interindividual variability in pharmacokinetic parameters. The coefficient of variation, which measures the amount of variation in a data set, reached 61% for t_{max}, 65% for C_{max}, 68% for C_{min}, 65% for $AUC_{0-\delta}$ and 31% for $t_{1/2}$.

SAFETY

Results of the phase Ia multiple-rising-dose study in healthy volunteers of BI-201335 at doses of 20-240 mg once daily for 21-28 days demonstrated that the drug was safe and well tolerated and justified continuation into phase Ib (26). These results have not yet been published. In a phase Ib multiple-ascending-dose study of BI-201335 in 34 treatment-naive and 19 treatment-experienced patients, the drug was generally well tolerated. During the first 14 days during which the drug was administered as monotherapy, the frequency of adverse events was not higher in the BI-201335 group compared to the placebo group. Dose-dependent, mild unconjugated hyperbilirubinemia occurred with BI-201335, with a maximal median increase of 0.8 mg/dL in the 24-mg once daily group. When BI-201335 was combined with pegIFN/RBV, the most common adverse events were fatigue, nausea, headache, gastrointestinal discomfort and anemia. Four patients experienced a mild rash or photosensitivity that spontaneously resolved. Two severe adverse events (SAEs) were reported (asthenia and cataract), both of which were thought to be unrelated to BI-201335.

In a phase Ib trial of BI-201335 in HCV genotype 1 patients with compensated liver cirrhosis and prior non-response to pegIFN/RBV (29), there was good safety and tolerability in the once daily dosing group, comparable to non-cirrhotic patients (26). Isolated unconjugated hyperbilirubinemia was more common and more pronounced in the group that received twice daily dosing. Two severe adverse events and two treatment discontinuations occurred in the twice daily dosing group. In the interferon-free SOUND-C1 trial (discussed below), the reported adverse events during the first 28 days were mild gastrointestinal effects (diarrhea, nausea and vomiting), rash and photosensitivity.

In the phase IIb trials, several adverse events were reported in a higher proportion of patients receiving BI-201335 compared to those on placebo and were dose-dependent (27, 28). Jaundice, skin manifestations, including rash, photosensitivity reactions, pruritus and dry skin, and gastrointestinal side effects, mostly nausea, vomiting and diarrhea, were reported in the BI-201335 arms in a proportion exceeding 10% of the placebo/pegIFN/RBV group. Jaundice was secondary to predominantly indirect or unconjugated hyperbilirubinemia. The mechanism of action of this unconjugated hyperbilirubinemia is inhibition of hepatic uptake of UDP-glucuronosyltransferase 1-1 (*UGT1A1*) (30). In all trials of BI-201335, hyperbilirubinemia was dose-dependent, unconjugated, isolated and rapidly reversible at the time of drug discontinuation.

CLINICAL STUDIES

Activity in cell culture is usually predictive of in vivo efficacy. As previously discussed, BI-201335 exhibited similar and strong activity in enzymatic and cellular assays (25). The results of a phase Ib multiple-ascending-dose study of BI-201335 in 34 treatment-naive patients with HCV genotype 1 and 19 treatment-experienced patients were recently published (26). In this study, the treatment-naive patients were randomized to BI-201335 monotherapy 20-240 mg once daily versus placebo for 14 days, followed by combination with pegIFN/RBV for 14 days when a ≥ 1 $\log_{10}$ international units (IU)/mL decline in HCV RNA was reached following 14 days of treat-

ment. The treatment-experienced patients received 48-240 mg of BI-2101335 once daily in combination with pegIFN/RBV for 28 days. Monotherapy was not allowed in this group. All patients receiving BI-201335 (n = 25; 96%), except one in the 20-mg treatment group, achieved the primary efficacy endpoint of ≥ 2 $\log_{10}$ IU/mL HCV RNA reduction in the first 14 days. Among treatment-naive patients, median maximal HCV RNA reductions during 14-day monotherapy were −3.0, −3.6, −3.7 and −4.4 $\log_{10}$ IU/mL for the 20-, 48-, 120- and 240-mg groups. This −4.4 $\log_{10}$ IU/mL median maximal decline in HCV RNA at the dose of 240 mg once daily is comparable to what has been reported with telaprevir (maximal median decline of −4.4 $\log_{10}$ IU/mL at 750 mg every 8 hours for 14 days) (31) and boceprevir (maximal mean HCV RNA decline of −2.06 $\log_{10}$ IU/mL at 400 mg 3 times daily for 14 days) (32). As expected with protease inhibitor monotherapy, virological breakthrough occurred in most of the patients in the first 14 days. The proportion of patients with viral breakthrough by day 14 was 83.3%, 71.4%, 71.4% and 83.3%, respectively, in the 20-, 48-, 120- and 240-mg BI-201335 groups. At the time of breakthrough, NS3/NS4A-resistant variants (R155K with HCV genotype 1a and D168V with HCV genotype 1b) known to confer in vitro resistance to BI-201335 were found. When the R155K mutation was selected, sensitivity to BI-201335 was less, with EC_{50} values of 1.8-6.5 µM, whereas the EC_{50} for D168V mutants was 3.6-15 µM. These variants are also selected with the use of other protease inhibitors, such as the first-generation, first-wave protease inhibitors boceprevir and telaprevir, which strongly suggests cross-resistance (33-35). Second-generation protease inhibitors, such as MK-5172, which has pan-genotypic activity, do not share the same resistance mutations and retain activity against common first-generation protease inhibitor resistance-associated variants. It is known that naturally occurring variants resistant to HCV protease inhibitors exist in about 2% of treatment-naive patients at baseline (V36M, R155K, V170A and R109K) (36). The effect of pre-existing resistant mutants in patients treated with BI-201335 has not yet been reported.

Following 14 days of monotherapy, pegIFN/RBV was added in those patients with a ≥ 1 $\log_{10}$ IU/mL reduction in HCV RNA at day 6 or day 10, which was seen in all patients on BI-201335, but in none of the patients on placebo. After addition of pegIFN/RBV, 4 of 6, 4 of 7, 6 of 7 and 6 of 6 patients, respectively, treated with BI-201335 at 20, 48, 120 or 240 mg showed ≥ 1 $\log_{10}$ IU/mL HCV RNA reductions between day 15 and 28. Of the 19 treatment-experienced patients treated with BI-201335 and pegIFN/RBV, 3 of 6, 4 of 7 and 5 of 6 patients, respectively, in the 48-, 120- and 240-mg dose groups achieved HCV RNA < 25 IU/mL at day 28. All patients achieved the primary efficacy endpoint of ≥ 2 $\log_{10}$ IU/mL reduction in HCV RNA from baseline during treatment. The mean HCV RNA reduction was 5.3 $\log_{10}$ IU/mL for BI-201335 given as 240 mg once daily after 28 days in combination with pegIFN/RBV. Of the 19 patients, 3 experienced virological breakthrough during triple combination, but none in the 240 mg once daily group.

A different phase Ib trial assessed safety, short-term efficacy and pharmacokinetics of BI-201335 in HCV genotype 1 patients with compensated liver cirrhosis and prior partial response (maximum HCV RNA reduction > 1 $\log_{10}$ IU/mL from baseline but never achieved undetectable HCV RNA at any time) or null response (maximum HCV RNA reduction < 1 $\log_{10}$ IU/mL from baseline at any time) to pegIFN/RBV therapy (29). This was an open-label, sequential-group, dose-escalating comparison of 240 mg BI-201335 once daily (n = 6) or twice daily (n = 7) for 28 days in combination with pegIFN/RBV. All patients showed a rapid and continuous decline in HCV RNA, with mean HCV RNA declines on day 28 of −4.8 and −5.0 $\log_{10}$ IU/mL, respectively, in the 240-mg once daily and twice daily groups. At day 28, 5 of 6 and 6 of 7 patients achieved HCV RNA < 25 IU/mL in the once daily and twice daily groups.

SOUND-C1 was a phase Ib study that evaluated an interferon-free regimen consisting of BI-201335, BI-207127 (an NS5B inhibitor) and RBV in patients with HCV genotype 1, naive to HCV treatment. This was a randomized, open-label trial evaluating the combination of BI-201335 120 mg once daily plus BI-207127 400 or 600 mg 3 times daily and weight-based RBV (in 2 divided doses) for 28 days. At day 29, patients were switched to BI-201335 in combination with pegIFN and RBV, as specified in the protocol. The 28-day results have been presented (37). All but two patients experienced a rapid first-phase decline in HCV viral load in the first 2 days, followed by a slower second-phase decline. Patients with HCV genotype 1a had lower response rates when receiving BI-207127 400 mg three times daily compared to patients with HCV genotype 1b, while HCV subtype did not impact response rates in those receiving the dose of 600 mg three times daily. In the lower dose group, 4 of 15 patients had undetectable HCV RNA (< 25 IU/mL) at day 8, 6 of 15 at day 15, 10 of 15 at day 22 and 11 of 15 at day 29. In the higher dose group, at the same time points, 3 of 17, 14 of 17, 17 of 17 and 17 of 17 patients, respectively, had undetectable HCV RNA.

The phase IIb SILEN-C1 trial was conducted in patients with HCV genotype 1 naive to HCV treatment to evaluate the safety and efficacy of BI-201335 given once daily at a dose of 120 or 240 mg for 24 weeks in combination with pegIFN and RBV for 24 versus 48 weeks (27). A lead-in of pegIFN and RBV for 3 days was also evaluated in two of the four arms (with 120 and 240 mg once daily). In the two arms using BI-201335 at a dose of 240 mg (with and without a lead-in), patients achieving extended rapid virological response (eRVR) were re-randomized to either stop treatment at week 24 or continue with pegIFN/RBV for a total of 48 weeks. Patients receiving 240 mg once daily without a lead-in achieved the highest eRVR rate of 87% and were thus eligible for shortened treatment duration. This arm had the highest SVR rate of 83% versus 73% of patients receiving 240 mg with a lead-in and 56% of patients in the pegIFN/RBV control group. Prolonging treatment to 48 weeks in those patients achieving eRVR did not result in higher SVR rates. Of those who completed 24 weeks, 93% achieved SVR versus 90% of those who completed 48 weeks. Viral breakthroughs occurred in 2.8-5.8% of patients receiving BI-201335, with the highest rate in those in the 120-mg daily with lead-in arm. There was no difference in SVR according to HCV genotype 1 subtypes. In the 240-mg once daily arm, 82% of patients infected with HCV genotype 1a achieved SVR compared to 84% of those infected with HCV genotype 1b (38).

The phase IIb SILEN-C2 trial evaluated BI-201335 for 24 weeks in combination with pegIFN/RBV for 24 versus 48 weeks, with or without a 3-day lead-in of pegIFN/RBV in previous partial and null responders infected with HCV genotype 1 (28). The dose of 240 mg once daily (with and without a lead-in) was compared to 240 mg twice daily with a lead-in. Patients in the 240-mg once daily group

with lead-in achieving eRVR were re-randomized to stopping therapy or continuing 48 weeks with pegIFN/RBV. Similar to the SILEN-C1 trial, the lead-in did not appear to be useful. The 240-mg once daily dosing without a lead-in led to the highest SVR rates. Overall, eRVR was achieved by 45% of patients and SVR was achieved by 27-41% of patients. The lowest SVR rate was observed in the 240-mg once daily with lead-in arm, the one group that used response-guided therapy (RGT) for those achieving eRVR. In comparison to the good results observed with 24 weeks of treatment in the naive patients achieving eRVR in the SILEN-C1 trial (27), prior partial and null responders achieving eRVR in SILEN-C2 achieved lower SVR rates when stopped at week 24. Only 40% of patients achieved SVR when stopped at week 24 compared to 72% of those who completed 48 weeks of treatment. The additional 24 weeks of pegIFN/RBV greatly impacted the relapse rate. Sixty percent of those who stopped at week 24 relapsed compared to 21% of those who completed 48 weeks of treatment. Viral breakthroughs occurred predominantly on BI-201335 compared to pegIFN/RBV (17-28% vs. 5-7%).

SILEN-C3 was an open-label phase IIb study in treatment-naive HCV genotype 1 patients (39). The objective was to evaluate the efficacy and safety of 12 versus 24 weeks of BI-201335 with RGT. Seventy-nine patients were randomized to 120 mg BI-201335 once daily with pegIFN/RBV for 24 weeks followed by pegIFN/RBV alone for up to 48 weeks. Eighty-one patients were randomized to 120 mg BI-201335 once daily with pegIFN/RBV for 12 weeks followed by pegIFN/RBV alone for a total of 24-48 weeks. The total duration of pegIFN/RBV tail depended on achievement of eRVR (HCV RNA below lower limit of quantification at week 4 and HCV RNA below lower limit of detection from week 8 to 18). In the 12-week triple therapy arm, 65% of patients achieved SVR compared to 73% of those who received 24 weeks of triple therapy. More than 70% of patients achieved eRVR and received 24 weeks of total treatment.

Currently, patients are being recruited in phase III clinical trials. In treatment-naive patients with HCV genotype 1, a randomized, double-blind, placebo-controlled phase III study of once-daily BI-201335 120 mg for 12 or 24 weeks or BI-201335 240 mg for 12 weeks in combination with pegIFN/RBV will enroll 625 patients. A different randomized, double-blind, placebo-controlled phase III study also in treatment-naive patients will enroll 625 patients to compare BI-201335 120 mg once daily for 24 weeks to 240 mg once daily for 12 weeks in combination with pegIFN/RBV. In treatment-experienced patients with HCV genotype 1, a randomized, double-blind, placebo-controlled phase III study of BI-201335 240 mg once daily for 12 or 24 weeks in combination with pegIFN/RBV will enroll 625 patients.

In HIV/HCV co-infected patients, a multinational phase III trial started enrollment in the fall of 2011. This trial is evaluating the efficacy and the safety of BI-201335 for 12 or 24 weeks in combination with pegIFN/RBV for 24-48 weeks in HCV treatment-naive patients or prior relapsers who are co-infected with HIV. This trial is among the first to evaluate a shorter than 48-week treatment (response-guided therapy) with DAA in HIV co-infected patients.

DRUG INTERACTIONS

Three different drug interaction studies of BI-201335 have been conducted evaluating potential drug interactions with darunavir/ritonavir, tenofovir and efavirenz. The results have not yet been published.

SOURCE

Boehringer Ingelheim Pharma GmbH & Co. KG (DE).

DISCLOSURES

The author states no conflicts of interest.

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